EDINBURGH POST-GRADUATE LECTURES IN MEDICINE

VOLUME THREE

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FOREWORD

THESE Post-Graduate Lectures, which illustrate some of the activities of the Edinburgh School, have been delivered at regular intervals throughout the war, despite the absence of a number of our potential lecturers on military service. The publication of this, the third, volume, which contains thirty-two lectures, and a fourth volume which is in type and will soon appear, has however been delayed by the paper shortage. Our thanks are due to Professor D. M. Lyon for seeing these volumes through the press.

Post-Graduate teaching, which was almost in abeyance during the war, has been resumed and on a much more elaborate and extensive scale than in the pre-war days.

The Post-Graduate Committee, which had been responsible for our arrangements during the past forty years, was replaced a few months ago by an official Post-Graduate Board under the direct ægis of the University and our two Royal Colleges. We recognise that Post-Graduate teaching is of great importance and must be conducted throughout the year on a basis which will bear comparison with our reputation as an undergraduate school. Ten weeks' courses both in Medicine and Surgery are now in progress in addition to short refresher courses of a fortnight's duration for general practitioners.

EDWIN BRAMWELL
Chairman of the late Post-Graduate
Executive Committee

May 1946

The Committee, which nominates and invites the lecturers, consists of the Professors of the Practice of Physics, Systematic Surgery, and Obstetrics in the University; the Presidents of the Royal College of Physicians and of the Royal College of Surgeons; the Senior non-professorial Physician and Surgeon on the Staff of the Royal Infirmary; the Editor of the *Edinburgh Medical Journal*, and the Chairman of the Post-Graduate Executive Committee (Convener).

THE CONTRIBUTION OF THE EMERGENCY MEDICAL SERVICE TO MEDICINE AND SURGERY IN SCOTLAND

By ANDREW DAVIDSON, M.D., D.P.H.
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I. Introduction

THE development of the country's health services has been an evolutionary process extending over rather more than one hundred years of progress, but mainly crowded into the period since the beginning of this century Most of our present schemes comprising these services have originated in voluntary effort, and only after many years have they been officially recognised in legislation. The story of the development of anti-tuberculosis measures is an example. Here, in Edinburgh, the first tuberculosis dispensary was established in 1887 by Sir Robert Philip; yet it was not until a quarter of a century later that legislation gave official recognition to such a provision. A similar story might be told in regard to maternity and child welfare work and to other schemes. There is the "break-up of the Poor Law," with the transference of its health functions to health authorities, which was recommended by a Royal Commission in 1909, but which did not become official policy until twenty years afterwards Now we read of the "health centre" in the new proposals for post-war reorganisation of the health services; more than twenty years have elapsed since the Consultative Committee on Medical and Allied Services of the Ministry of Health recommended such a unit and its provision is still a recommendation. In administration, even more than in clinical work, there is apt to be a gap between new conception and general adoption. But there are times when it is necessary to take immediate steps to secure legislation for urgent health problems; and in war-time particularly there is provision for such contingencies, if not by special enactment then by a defence regulation, as was the case with the Venereal Diseases Regulations, 1916. It is during war that the close relationship between the physical and

Read 30th July 1942

mental fitness of the people, their morale, their productive capacity, and, in general, their ability to defend their rights and privileges is best appreciated. The health services then become a most important integral part of the war machine and the tempo of their development is quickened. The establishment of the Emergency Medical Service is a good example of the creation and rapid development of a new health service to meet an urgent demand. The organisation and gradual expansion of this service to its present high standard of efficiency within the relatively short period of four years is such a remarkable achievement and of such potential value that it will be appraised, in due course, as one of the outstanding events in the medical history of Scotland. Its story will be recorded in the official Medical History of the War, but, even now, many of its accomplishments may be evaluated. The "E.M.S.," as the service is tabbed, has a wider significance than its name implies, for not only does it comprise the establishment of a medical service as such, but it also includes the provision of a hospital service with all that this involves.

The preparation of the medical arrangements for this new service in anticipation of war was a task of complexity and magnitude In Scotland, however, it was fortunate that there was some authentic information regarding the weaknesses in the health services, as several committees had considered these matters, particularly the problem of hospital accommodation, in the period since the last war. The availability of this information and other factors, such as the ease with which the country divides itself into regions suitable for hospital administration, the convenient size of Scotland as a national unit and the whole-hearted support given to the Department of Health by local authorities, by voluntary hospitals and by all branches of the medical and nursing professions, combined to minimise the difficulties of providing a national hospital service for war-time purposes. This all-round spirit of co-operation is a happy augury for the post-war reorganisation of the country's health services, which most people are agreed is necessary.

It would be impossible in one lecture to describe all the details of construction, development and operation of the Emergency Medical Service, and therefore I propose to confine my remarks to an outline of some of its main contributions to medicine and surgery in Scotland.

II. The Pre-War Hospital Provision in Scotland

It was indeed fortunate that at the outbreak of war there was in existence a full report on the Scottish health services (1936). This report was one of the best products of its kind and its scope extended over every aspect of the health services of the country. In regard to hospitals, it pointed out that a serious shortage of hospital facilities had continued for a long time; that an adequate hospital service was essential for the public health; and that steps should be taken to provide it. Before the outbreak of war it was estimated that there was a deficiency of 3600 hospital beds in the country for normal peace-time requirements. It became evident, therefore, that, if the new responsibilities for the treatment of war casualties were to be effectively carried out, there was no alternative to the building of new accommodation and, if possible, regionally. The only problem then was to consider how much new accommodation was required and the ways and means of obtaining it.

There has never been any disagreement on the question of the regionalisation of the country for hospital purposes. Scotland divides itself geographically into five regions, four of which are centred on the University Medical Schools while the fifth is centred on Inverness. The new hospital organisation for emergency purposes was subsequently to be built round these five regions in each of which a Regional Hospital Office was established. The following table shows the hospital position in Scotland at the beginning of 1938:—

Pre-War Hospital Accommodation in Scotland

Region.	Centre.	Number of Hospitals.			Number of Beds		
		Local Authority	Voluntary	Total.	Local Authority	Voluntary	Total
Northern . .	Inverness	22	18	40	666	501	1,167
North-Eastern.	Aberdeen	27	28	55	1,471	1,379	2,850
Eastern .	Dundee	33	39	72	2,050	1,732	3,782
South-Eastern .	Edinburgh	48	44	92	3,985	3,319	7,304
Western . .	Glasgow .	126	90	216	12,848	7,145	19,993
All Scotland . .		256	219	475	21,020*	14,076	35,096

* Includes only 4362 beds in general wards

III. Evolution of the Emergency Hospital Service

The Emergency Hospital Service was organised and developed under the Civil Defence Act of 1939. The Act made the Secretary of State for Scotland responsible for securing hospital treatment for casualties arising from enemy attack; and this responsibility is discharged through the Department of Health for Scotland. The Committee on Scottish Health Services commented in various parts of its report on the insufficiency of hospital facilities for maternity, orthopædics and other purposes. The report also stated that there was a corresponding deficiency of facilities for general medicine and surgery, and it was this deficiency which made it imperative to develop, as a matter of urgency, a hospital system capable of meeting such casualty needs as might arise. Various methods were adopted for obtaining the urgent accommodation necessary. They comprised the provision of new hospitals, some from the ground upwards, others centred round country houses, the conversion of two hotels and a training college for the purposes of surgical hospitals; the upgrading of selected hospitals, mental institutions and smaller hospitals by providing hutted annexes, operating theatres and other essential equipment for hospital purposes; the use of 62 large private houses, kindly given by their owners for use as auxiliary hospitals; the use of four convalescent homes; and finally, the provision of additional bedsteads either to be erected immediately by reducing the standard of accommodation within limits or for erection during emergency The new emergency hospital accommodation provided for war purposes comprised .—

I *Beds in General Hospitals*

New Hospitals	Hutted Annexes.	Converted Hotels	Other.	Total.
7038	8526	910	100	16,574

II *Beds in Convalescent*

Large Country Houses.	Miscellaneous.	
3426	527	3,953
	Grand Total	20,527

The total bed accommodation thus provided was 20,527 beds, of which 16,574 were for general hospital purposes and 3953 for convalescent purposes This new accommodation represents close on 60 per cent. increase in bed accommodation throughout the country.

The provision of accommodation was a simpler problem than the staffing of that accommodation or its equipment. It is obvious that the medical and nursing staffing for this large increase in hospital accommodation was a problem of some magnitude. That it has been solved satisfactorily is due in large measure to the patriotic response of both the medical and the nursing professions and the very willing help given by their associations. The E.M.S. has been responsible, among other things, for bringing all branches of the medical profession into more effective co-operation than formerly; this co-operation will help substantially to establish and to develop the team-work so necessary to the successful working of the health services of the present and of the future. The number of doctors enrolled in the E.M.S. on the 30th September 1943 were:—whole-time medical officers 144; part-time visiting medical officers on a salaried basis 142; part-time medical officers on a sessional basis 840; junior house officers 31—a total of 1157; in addition, many specialists have given their services gratuitously. This medical staff is distributed over every speciality.

The nursing problem was a major one and involved the establishment of the Civil Nursing Reserve. As in the case of doctors the response of nurses was excellent and a large complement of nursing personnel has been established. This reserve comprises 860 trained nurses, 554 assistant nurses and 3091 nursing auxiliaries, but does not include nurses normally in civilian employment. No matter how important doctors and nurses may be, no hospital can function without staff of other designations. Stewards, domestic staff, technicians of various kinds, porters, engineers and others were all required. There have been difficulties of staffing, mainly arising from the general problem of man and woman power, but perhaps the greatest of these has been in relation to domestic staff. Still, the hospitals have fulfilled satisfactorily all demands made upon their services. On the 1st October 1943 there were 7573 patients under treatment in E.M.S. hospitals. At the beginning, the equipment was essentially of an emergency character, but with the gradual development of these hospitals as general hospitals the equipment has been brought up to the level necessary for the additional responsibilities. It has been found necessary to provide consumable medical supplies from central stores. This arrangement and the maintenance of equipment have required much forethought and organisation. One of the consequences of this rapid develop-

ment of hospital accommodation throughout the country has been that the Department of Health for Scotland has become a hospital authority and now administers nine base hospitals and sixty-six auxiliary and convalescent hospitals.

The emergency hospital accommodation was originally intended for war casualties, both military and civilian, but the list of scheme patients now includes thirty different categories—for example, transferred essential war workers, patients from voluntary hospital waiting lists, war industry fractures, emergency cases and others. The effect of widening the scope of admission is that all types of case, except what is known as "chronic" illness, are treated in E M.S. hospitals.

IV. Regionalisation of Hospital Facilities

Several committees have recommended the regionalisation of hospital facilities and have emphasised the need for the closest co-operation between the boards of voluntary hospitals and local authorities. Indeed, both these matters were included in the Government's recent announcement on the broad lines of their post-war hospital policy. The E.M.S organisation in Scotland has already been built up on a regional basis with a Regional Hospital Office in each of the five regions.

Also, special units have been organised regionally in seventeen separate hospitals, for example, units for such special purposes as brain surgery, peripheral nerve surgery, orthopædics, face and jaw injuries, effort syndrome, eye injuries, thoracic injuries and gas casualties, have been regionalised. The establishment of a neuro-surgical unit in the West of Scotland has often been quoted as an interesting development in regionalisation as it involves co-operation between the Corporation of Glasgow and the three medical teaching schools of the City in the establishment of a unit for neuro-surgery at one of the Department of Health hospitals. In this case there has been a pooling of resources in medical and nursing personnel and in equipment. This arrangement is another happy development which should be an example for future reorganisation.

V. Co-operation with Other Authorities

A striking feature of the Emergency Hospital arrangements has been the co-operation between all interested hospital authorities and their staffs. In addition, the closest co-operation

has been maintained with the medical departments of the fighting services. An example of this close co-operation is the establishment of an Army Hospital Unit in an E.M.S. hospital mainly for training purposes; another example is the installation of a whole sanatorium unit, administered by a Joint Board of Local Authorities, in an E.M.S. hospital; other examples are to be found in the admission to E.M.S. hospitals of cases normally treated in voluntary and municipal hospitals. There is even a tentative arrangement for the establishment of facilities for treating cancer at one of the new country hospitals in the event of damage to certain voluntary hospitals where such treatment is now provided. All these forms of co-operation have been gradually evolved in the best spirit all round, and the existence of this spirit of co-operation should make easier the ultimate reorganisation of the hospital system of the country.

We have also been able to provide, in two E.M.S. hospitals, accommodation for our Polish and Norwegian Allies; in each case the hospital unit is administered by medical personnel of these nations.

VI. National Orthopædic Service

The E.M.S was established to provide hospital treatment for casualties; this immediately suggested the organisation of facilities for orthopædic treatment. From this origin there has gradually developed the skeleton of a national orthopædic scheme. Before the war, only one or two of the larger hospitals in Scotland had developed fracture departments Recognising the shortage of facilities and the certainty that the war would greatly increase the number of cases requiring care and treatment, the Department of Health proceeded to make arrangements for the concentration of fracture cases, for which it is responsible, under expert care at a few of its casualty hospitals. Orthopædic centres for the purpose were accordingly established at seven hospitals and a total of 2200 beds was set apart for this purpose These hospitals are suitably distributed throughout the country. A specialist staff has been engaged for each hospital; each unit has also been supplied with the necessary equipment for physio-therapy and medical gymnastics on the lines advised by the orthopædic consultants, while, in addition, handicraft workshops for occupational therapy have been provided and equipped; a scheme of follow-up clinics is being set up in conjunction with the main orthopædic centres. We now have a national orthopædic scheme

in the making, and this, in itself, is a substantial contribution to surgery in Scotland. The future possibilities have been foreseen, as regional orthopædic councils have been established throughout the country and their work is being co-ordinated by a Scottish Orthopædic Council. However valuable it may be, the provision of hospital accommodation is not the only requirement of a well-organised orthopædic scheme. The essentials of the complete scheme are arrangements for early ascertainment, the provision of facilities for treatment by clinical methods, occupational therapy and rehabilitation, followed by vocational training and the placement of trainees in employment. This comprehensive range of requirements directed towards the welfare of the cripple implies, in addition to hospital accommodation and treatment, the establishment of clinics and workshops linked up with the pivotal hospital on the one hand, and, on the other, with those organisations, both voluntary and statutory, responsible for the welfare of the cripple. Much progress has already been made in attacking all these aspects of the problem, and there is gradually emerging a compact and highly organised national orthopædic scheme which will be of outstanding value in the post-war period.

VII. *Blood Transfusion and Infusion Fluids*

A corollary to the extension of hospital facilities to deal with war casualties was the need to provide certain essential facilities for the treatment of shock, and, in particular, facilities for blood transfusion and for infusion

Early in 1939 the Scientific Advisory Committee of the Department of Health undertook preliminary work in surveying the existing blood transfusion services and encouraging, where necessary, their expansion, including the setting up of committees at various centres for the recruitment of donors and depôts for the storage of blood in the main cities. At the outbreak of war, emergency transfusion services came into operation in the various regions of the country In February 1940 the National Blood Transfusion Association was formed to co-ordinate the work being done in the various regions The association is a voluntary body receiving assistance by grant from the Department of Health. The Central Council is directional and advisory, while, in each region, there is a committee responsible for local administration ; a regional director is responsible for the grouping of donors, the withdrawal, preparation and storage of blood at the blood

bank and its supply with appropriate equipment to the various hospitals. The director has the assistance of an organiser and voluntary staff undertaking propaganda, the recruitment and recording of donors and the raising of funds. In 1941 a further development was the establishment of centres at Edinburgh and Glasgow for the preparation of filtered plasma, and in 1942 a drying plant was put into operation at the Edinburgh depôt.

The blood transfusion service is catering not only for war casualties, civil and service, but also for normal "peace-time" patients. The work is developing and has come to stay as part of the country's medical service.

Apart from the provision of blood and blood products, it was also essential to ensure that there would be available in emergency an adequate supply of infusion fluids. The Department of Health created an infusion service and has supplied the necessary equipment to emergency hospitals; at centres located in the principal cities infusion fluids are produced under strictly controlled laboratory conditions. Unlike the transfusion service, the infusion fluids are provided solely for emergency use.

VIII. In the Field of Preventive Medicine

It is perhaps in the field of preventive medicine that some of the more interesting work is being done in the E.M.S. hospitals.

(i) **Treatment of Tuberculous Persons.**—The incidence of tuberculosis is one of the sensitive indices of war-time conditions. As in the last war, the number of cases of tuberculosis has increased, and heavy demands have been made on accommodation in tuberculosis hospitals and sanatoria. Additional accommodation has been made available in E.M.S. hospitals for the treatment of tuberculous persons. Unfortunately, at the outbreak of war, it was necessary to encroach on the accommodation for tuberculous persons; the resulting loss, however, has been more than made good, and at the end of September 1943 there are, in fact, some 850 more beds being used for the treatment of tuberculosis than before the war. A reference has already been made to the inclusion of a whole sanatorium unit in an E.M.S. hospital.

(ii) **Supervision of Health of War Workers.**—That there is great need for supervision of the health of industrial workers has long been recognised and war has once more drawn urgent attention to that need. In the first place, it is of the utmost importance to the nation to secure maximum industrial output

and that end can only be reached if the workers are maintained in a healthy state. Secondly, large numbers of workers—especially young women—wholly unaccustomed to factory conditions have been absorbed into industry; and the strain of work with such additional adverse effects of war-time conditions as long hours, blackout, travelling and feeding difficulties, combine to produce conditions which may well lead to mental or physical breakdown.

Early in 1942 an experimental preventive scheme was set up in the Clyde basin for the benefit of young industrial workers in that area. The essence of the experiment is prevention of those physical and mental breakdowns which on occasion result in long periods of incapacity. The main objects are to detect early signs of breakdown and to counteract these at once by suitable action; and any facilities provided are supplementary to existing arrangements.

Originally, the scope of the experiment was limited in two directions First, it dealt for the most part with young industrial war workers and particularly with those between fifteen and twenty-five years, because this age group was thought to be most likely to react unfavourably to war-time factory conditions. Secondly, the experiment was restricted to the Clyde basin, *i e* the City of Glasgow and the counties of Dunbarton, Renfrew and Lanark. The reasons for this latter restriction were (*a*) a total of 896,000 workers or 44 per cent. of the total insured population of Scotland lives in this area; (*b*) pre-war sickness rates were high; (*c*) a skeleton Regional Medical Officer service for National Health Insurance purposes was available, supported by a wide range of expert services provided by skilled specialists of all kinds attached to the Glasgow teaching hospitals, (*d*) the Department of Health's new hospitals at Killearn (640 beds), Law (1280 beds) and Ballochmyle (1280 beds) situated nearby in the country were capable of providing sufficient beds, whilst hospital specialists for all purposes were available to carry out thorough medical investigation where this was required; (*e*) finally, auxiliary accommodation for convalescence was available at a number of convalescent homes, attached to these hospitals, where cases could recuperate in country surroundings and have the benefit of medical supervision, rest and good feeding On 1st December 1942 the scheme was extended to apply to the whole industrial belt of Scotland, and the age restriction was withdrawn.

The principal type of case seen is the young, debilitated

worker in whom little, if anything, in the nature of gross organic disease is found. A proportion shows conditions which may partly or wholly account for the symptoms (*e.g.* anæmia, unsatisfactory dental or tonsillar states); others again have recently had and are convalescing from fairly well-defined diseases (*e.g.* influenza, pleurisy, pneumonia); a few are contacts with persons suffering from tuberculosis who, on being referred to tuberculosis officers, have been found free from the disease; but the greater number have merely vague general complaints of undue fatigue, vague aches and pains, loss of appetite and so on.

Numerically, the next most important group of cases includes those suffering from anxiety states and persons with repeated attacks of relatively minor respiratory illnesses whose period of recuperation has been prolonged. In the histories of these patients a collection of circumstances of possible etiological significance is found; for example, long hours of work, uncongenial work, industrial misfits, changing shifts, excessive travelling, unsatisfactory diet (in spite of the provision of canteens), over-indulgence in tobacco, etc.; but it is usually impossible to indicate in the individual case the relative importance of these factors. Late hours in ill-spent leisure have not been prominent in the series of young workers examined in the scheme.

Many patients require only a period of rest, a change of scene and good feeding for restoration—at least temporarily—to fitness for work; in others, ordinary clinical overhaul still leaves doubt as to the absence of more serious underlying disease. Where a period of convalescence is indicated, this is provided under the scheme; but where there is the least doubt about the presence or nature of more serious disease the patients are first admitted to hospital, where anything further required for diagnosis is readily available. The reassurance of absence of major disease is naturally also a potent factor in expediting return to full fitness especially in the anxiety states.

The number of workers who have passed through this scheme from its inception in January 1942 to 30th September 1943 was 5151; of that number, about 60 per cent have been treated in hospitals and convalescent homes. It is hoped that the numbers will increase for, so far, reports of patients discharged from hospital or convalescent home leave no doubt of the benefits to the individual of the treatment afforded, and there must be many more who might benefit.

The after-care of these young patients is of great importance,

as any procedure seeking to safeguard the health of industrial workers, however valuable, may have its usefulness limited unless it is associated with a mechanism for securing review of the work of the individual in relation to his physical condition. Consideration is being given to the question of how best to obtain the necessary linkage with industrial placement in any development of this experiment.

(iii) **Rehabilitation.**—Within recent years there has been developing a wider outlook on the treatment of disease and injury. Whereas formerly a patient was considered only from the clinical point of view, the new concept envisages the restoration of the patient to the highest degree of working capacity of which he is capable. The process of achieving this object is termed "rehabilitation" and it comprises the several stages of the treatment, physio-therapy, occupational therapy and vocational training; the last stage is not strictly medical, but nevertheless it is closely wrapped up with the medical aspect of the case and failure in that stage may prejudice the future of the patient. Some attention had been paid to the rehabilitation of *injured* patients, but nothing has been done in regard to the large numbers of persons suffering from *medical* disabilities This is a problem of some magnitude and of increasing importance

From 1930 to 1938 the problem of incapacitating sickness had been given much consideration by the Department of Health and a good deal of valuable information had been collected from National Health Insurance statistics. For example, in 1938 more than 11 million working days, or 44 per cent. of the total recorded incapacity, were due to incapacities which continued throughout the year. Analysis of these incapacities indicated that the number of cases per thousand insured males was 18·5 for organic mental and nervous disease; 11·1 for diseases of the respiratory system; 9·8 for diseases of the circulatory system; 9·4 for rheumatism and diseases of muscles and joints; 4·5 for diseases of the digestive system; 4·4 for tuberculosis and 3·6 for injuries These figures give an idea of the problem as it existed *before* the outbreak of war. In a special investigation carried out after the first year of war it was found that in 9000 men boarded out of the army in Scotland the disorders chiefly responsible for the disability were mental and nervous disease 24 per cent.; alimentary disease 21 per cent.; chest disease 16 per cent.; while injuries only comprised 4 per cent. It is clear, therefore, that there is a substantial untouched problem of rehabilitation for persons

suffering from medical disabilities. This problem opens up a wide field in social medicine; it is one which will increase as the war progresses and its importance may even become greater in post-war years.

At one of our E.M.S. hospitals careful attention has been paid to this subject and interesting information has been obtained in regard to the large series of cases discharged from the Services. Their replacement in industry has been carefully considered in collaboration with the Ministry of Labour, whose interim scheme for the employment of disabled persons has given a good opportunity for the development of this medico-industrial work. A beginning has recently been made with this kind of work in Scotland. In 1942 a series of 1000 consecutive men invalided out of the Forces as unfit for further service was followed up six months after return to civil life to see how the men fared medically, socially and in relation to employment. The results of this and other Scottish experiments are presented in a brochure, *Health and Industrial Efficiency*, published by the Department of Health for Scotland in 1943.

(iv) **Waiting Lists Scheme for Voluntary Hospitals.**—The pre-war shortage of beds in general hospitals throughout Scotland inevitably led to an increase in the length of waiting lists for treatment in voluntary hospitals. For various reasons it has never been possible to estimate accurately the numbers of patients awaiting admission to hospitals for treatment. Nevertheless the numbers were known to be substantial, and there seemed to be no defence of the position whereby on the one hand such large lists existed and on the other vacant accommodation was available in E.M.S. hospitals. This humanitarian aspect was not the only one, for the increasing industrial development for war purposes required the maximum amount of man and woman power. For these reasons, therefore, arrangements were made with voluntary hospitals to admit cases from their waiting lists to E.M.S. hospitals on generous financial terms. Since the beginning of the agreement nearly 22,000 patients have had treatment and their names removed from waiting lists; about 1200 "waiting list" patients are in emergency hospitals at any one time

(v) **Emergency Bacteriological Service.**—A survey carried out shortly before the outbreak of war revealed that facilities for bacteriology in relation to epidemiology, though perhaps reasonably adequate for peace-time needs, were in many instances strained very nearly to capacity. Sometimes the laboratories

were housed under conditions that made it impossible to expand to meet any sudden emergency, and ill-placed geographically to meet their existing obligations amid the disorganisations of war. Changes in territorial distribution were effected; existing laboratories were re-housed and some new ones created; a large reserve of equipment was acquired; transportable units were assembled and stored in places from which they could be mobilised at once to meet any epidemiological emergency. Personnel was supplemented so far as possible, and the service, under the guidance of the four Scottish Professors of Bacteriology as Regional Directors, took over the provision of public health bacteriological services throughout Scotland within a week of the outbreak of war. It is planned on regional lines; already it has been linked through its Regional Directors to hospital services; and there is reason to hope that war-time developments in this field will fit well into the pattern of health services in post-war years.

IX. Conclusion

My subject has been a departure from the usual clinical and scientific character of these lectures. It is mainly of an administrative nature, but its importance will be fully realised by all who are following the present trend of events in the medical world. I have tried to indicate the main contributions which our Emergency Medical Service has made to medicine and surgery in Scotland. It has been the means of providing, at short notice, the foundations of a national hospital service by the construction of much-needed new hospital accommodation, mainly in country surroundings; these foundations have been laid on a regional basis; it has brought together the various types of hospital authorities; it has brought various interests of the medical profession into successful co-operation; it has provided national schemes for such important services as orthopædics, bacteriology, blood transfusion and other specialities. Also, the Service has provided courses of instruction and inter-hospital discussions in several of the specialities undertaken by it, while clinical meetings for medical officers of the Forces and general practitioners have been held regularly in several E.M.S. hospitals. This instructional work is being fostered and extended.

These are no mean achievements, though a mere factual recital of them gives but a sketchy and inadequate impression of the everyday work of the Service. It scarcely touches the

teaching and the research in clinical, preventive and social medicine that do so much to set the standard of a service. What has been achieved, however, in all these directions, during the past four years, justifies the feeling that Scotland has now at hand, for the first time, more than the scaffolding of a first-class national hospital service. Two facts are clear, namely, that this new hospital accommodation is available in the country for post-war use, and the amount of that accommodation not only covers pre-war deficiencies but gives a wide margin of additional accommodation. Allowing for a better standard of bed spacing for post-war use, there should be available throughout the country about 13,000 new beds, half of them in entirely new hospitals, *i.e.* nearly four times the estimated pre-war deficiency. Indeed, with careful thought in planning new developments and extensions and with the continued goodwill and co-operation of all concerned in the E.M.S., there is no reason why Scotland should not emerge from this war with a national hospital service commensurate with its great traditions in medicine and surgery.

THE DIFFERENTIAL DIAGNOSIS OF THE CHRONIC AFFECTIONS OF THE LUNGS

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Anatomical.—The basis of the organs of respiration is the tubular airway. The wide upper tubes divide and subdivide to a fixed anatomical plan and reach finally the terminal bronchioles which pass into the systems of atria and air sacs which communicate with the alveoli. These bronchiolar ramifications are grouped into bundles which constitute the lung lobule, the basis of the pulmonary architecture. The lobules are in direct communication with the outer air and so with other lobules, and are held together by connective tissue rich in elastic fibres. These interlobular septa are continuous with the subpleural fibrous tissue and with that surrounding the bronchi and blood vessels.

The pulmonary artery accompanies the bronchus and follows its ramifications to end in the capillary networks which lie on the alveoli. The blood returns by corresponding venous channels tributary to the pulmonary veins. The subpleural vascular network is continuous with the pulmonary venules and also with the bronchial arterial terminations. The bronchial tubes and the connective tissue of the lung and pleura are supplied from the bronchial arteries, but most of their blood finally enters the return circuit of the pulmonary veins.

There are two groups of lung lymphatics, the perilobular lying around the veins in the interlobular septa, and the intralobular lying around the terminal bronchioles and bronchial arteries. There are no lymphatics in the walls of the air sacs and atria. The two groups communicate within the lobules, and the perilobular lymphatics communicate also with the subpleural lymphatic network The subpleural tissue is thus in vascular and lymphatic connection with the substance of the lung. Deposits of lymphoid tissue occur at points within the lobular system and are related to its respiratory elements. The bronchial lymphatics join the trunks from the deeper lobules which accompany the pulmonary vessels and bronchi, and end in the glands of the hilum; and the lymphatics which surround the superficial lobules return with the superficial collecting trunks which reach the

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hilum via the lung surface. These points have their pathological significance.

The glands in the lung roots are in five main groups. The paratracheal, the tracheobronchial and the bifurcation glands communicate with one another and with their opposite groups. The bronchopulmonary and pulmonary groups have no such communications.

Efficient pulmonary function depends upon the untrammelled action of the chest wall and diaphragm and upon an efficient cardiac mechanism—points which require no elaboration.

The Symptoms and Signs of Lung Disease.—Disease of the lung may be selective in its onset, but destruction or obstruction of one tissue overflows into another, and a lesion which originally was interstitial or parenchymatous may speedily become canalicular in its spread. The obverse as readily happens. There is thus a group of symptoms which is common to disease of the respiratory system, and the assessment of their significance may involve very great difficulties.

The chief of these is *cough*, Nature's effort to preserve the patency of the bronchial tree. The patency may be threatened by the pus of a destructive lung lesion or by the œdema of a failing heart, or it may be by the pressure of a lung or mediastinal growth or an aortic aneurism. It may vary in character from the loose productive cough of the open tuberculous lesion to the brassy stridor of the compressed airway. It may have its daily period of intensity as in the morning cough of the chronic lung cavity, or it may be incessant and painful and dry as in the cough of the early pleurisy or malignant growth. It is the patient's main symptom and much may be learned from its observation.

With the cough there is secretion, and the *spit* mug has a story to tell. The laboratory may provide the culture or the slide but the wise physician reads the tale at the bedside. From the fœtid ounces of advanced bronchial dilatation to the scanty blobs of bloody mucus of malignancy there are many gradations. They are there for all to see.

Destruction of lung or bronchial tissue, new growth, the pulmonary infarct, or the congestion of the failing heart may all produce *hæmoptysis*, which may vary from the streaks of chronic bronchial congestion to the pints of the ruptured cavity aneurysm. The term glorifies the one and does scant justice to the other. What comes up should be seen. A second's observation is worth an hour of hearsay.

No part of the body has a monopoly of *pain*, and pain in the chest may have a diagnostic significance. The stab of pleurisy, the nag of malignancy, and the agony of angina all have their characteristics. The patient's story is worthy of heed.

Dyspnœa, too, has its types. It may come unheralded with the rupture of a lung, or it may be the permanent accompaniment of an advanced fibrosis. It may be due initially to replacement or destruction of true respiratory tissue. In the end, the labouring right heart adds its quota. The stridor of bronchial compression proclaims itself, and the agony of asthma has its individual picture.

Some conditions have a monopoly of *physical signs*, and the ruptured lung and the gross effusion leave little room for doubt; but behind the air and the fluid other conditions may lurk. A lung abscess may be a necrotic cancer and an infiltrating carcinoma may give signs which mimic those of infiltrating tuberculosis. Extensive miliary tuberculous disease may have few physical signs and the deposits of cancer may fail to reveal themselves to the finger or ear Behind the signs, however, there lies the patient, and on him there is often stamped the individuality of his disease. He is the whole picture, and a quiet survey of him may reveal the significance of many things which superficially appear to be inconsistent.

Few diagnoses are complete without the *accessory aid* of the radiologist and of the pathologist, or his confrère the bacteriologist. They may confirm or refute the clinical findings. In some conditions their opinion is final. In others it is merely accessory. Where their views cut across a defined clinical picture they should be met in consultation. Their specialised services should not be employed to save clinical effort. They are helpful colleagues, not easy cuts to diagnosis. The value of the tomograph in isolating the deep lung lesion should not be forgotten.

Classification of disease is never easy, and I shall deal with diagnosis in wide terms. Some conditions are common and are recognised without difficulty Others are infrequent and for that reason are overlooked. A word on that indeterminate condition, chronic bronchitis, is a useful preliminary to discussion of diseases of the lungs themselves

Chronic Bronchitis.—It is very doubtful if a diagnosis of chronic bronchitis is ever justified, for the bronchial inflammation is almost invariably secondary to other conditions. It is an integral part of the group of fibroses, and it accompanies the

failing circulation or degenerating kidneys of advancing years. It goes with the emphysema of the years of maturity and decline, and senile phthisis often masquerades under its easy title. In the young it may be a manifestation of the silent but dripping nasal sinus.

Emphysema.—The emphysematous chest needs no description. The diagnosis is obvious, but what it conceals may be less so. It accompanies the increasing rigidity of the ageing thorax. Recent experimental work on this point is of interest (Paine, 1940), but it may also be an index of graver conditions.

Tuberculosis.—Tuberculosis respects neither age nor social status and its elimination rapidly narrows the field of diagnosis. It has its years of predilection and it has its symptoms which may outstrip the physical signs. The X-ray appearances are often diagnostic, and the presence of the organism in the sputum is final proof of the diagnosis. Arising as it often does in the upper lung fields the distribution of its signs is suggestive, but tuberculosis of the basal areas is far from rare. An X-ray film which shows much in relation to the physical signs supports a diagnosis of the disease. A film which shows little to account for gross signs should make us chary of the diagnosis. The failure to find tubercle bacilli during repeated examinations of a purulent spit makes the diagnosis improbable.

In the child the tuberculous lung infection is a different condition from that of the adult The primary focus either heals or extensive blood dissemination takes place. More rarely local extension leads to a clinical picture very like that of adult lung disease. The glands in the lung roots are always enlarged and may caseate, and they may provide many and varied symptoms and few physical signs On occasions they compress veins and bronchi, and less rarely lead to occlusion of a bronchus and partial lung collapse. In the absence of an extension of the local focus or of gross glandular pressure phenomena there are few physical signs, and one may say generally, and with truth, that extensive abnormal signs in a child's lung do not suggest tuberculosis. The child rarely produces sputum, but morning lavage of the fasting stomach may secure the swallowed blobs which provide material for smear and culture. Spreading lung disease, as in the adult, has its characteristic X-ray picture

Fibrosis of Childhood.—To be differentiated from tuberculosis is that condition of childhood known variously as *chronic non-tuberculous infection of the lungs* (Young, 1932), *pulmonary*

fibrosis (Gregory, 1927), *chronic influenzal fibrosis* (Wynn, 1927) and *chronic pulmonary catarrh* (Leys, 1927). The condition follows an attack of broncho-pneumonia and is a frequent sequel of measles and whooping-cough. Its end-result is bronchiectasis, and I shall consider it more fully under that heading. The history of the preceding illness is always definite, the signs are basal, usually unilateral, and tubercle bacilli are never found in the pulmonary secretion.

Bronchiectasis.—The conception of bronchiectasis has been widened in recent years, and it is recognised that there is a continuous process from early silent beginnings to the advanced fœtid terminal stage. Many theories have been advanced for its occurrence, but there is little doubt that it is associated very closely with pulmonary collapse (Lander and Davidson, 1938; Scott-Pinchin and Morlock, 1930 and 1933; Erwin, 1939). It is of interest that the condition up to a point is reversible and the dilated bronchi may return to their original state (Lander and Davidson, 1938). It usually dates from an attack of measles or whooping-cough or broncho-pneumonia in early childhood, and the typical story is that of recurring attacks of bronchitis and pneumonia, particularly in the colder periods of the year. The physical signs are of a composite and varying type according to the state of the bronchi, and they are liable to sudden changes with the onset of fresh infections. The children who form this clinical group have permanently established bronchial disease, and they furnish the material for the advanced state beloved of the text-books.

Another side to this gloomy picture is seen in that interesting type of bronchiectasis known as the *dry or hæmorrhagic type*—the forme hémoptoïque sêche (Burrell and Trail, 1930; Wall and Hoyle, 1933; Scott-Pinchin and Morlock, 1933; Lisle Punch, 1939). Patients with this condition may have trivial symptoms or no symptoms at all, and a big hæmorrhage or series of hæmorrhages may come without previous warning of ill-health. If symptoms have been present they are trivial—a little cough, scanty sputum, slight dyspnœa or transient pain in the chest. Hæmorrhage appears sooner or later in a majority and a diagnosis of tuberculosis may easily be made. The bleedings are often big and recur after symptomless intervals, and this intermittence of symptoms with a negative X-ray picture should raise a suspicion of the condition. These patients have histories of illness in early life similar to those of the previous group, but their symptoms

may not appear for intervals ranging up to twenty years after the inflammatory attack (Scott-Pinchin and Morlock, 1930). Some of them pass gradually into the infected and progressive group. Others remain well indefinitely. They are the obverse side of the gloomy prognostic picture of bronchiectasis. Injection of lipiodol into the bronchi will always establish the diagnosis.

The *secondary type of bronchiectasis* following inhalation of foreign bodies, the development of new growths, bronchial stricture, etc., is part of the primary pathological process.

Lung Collapse.—It is perhaps appropriate here to digress for a moment to the subject of lung collapse, which, although not itself a chronic condition, forms the basis of many conditions which are chronic. There have been many theories to account for massive collapse of the lungs, but there is one condition which always will produce collapse. That is the plugging of a bronchus, and there is now abundant evidence that this is the usual cause of the condition, the plugging agent being sticky sputum or blood from the lung. It is one of the risks of injection of the bronchi with viscid oils such as lipiodol (Scott-Pinchin and Morlock, 1931) The subject has been discussed in detail in recent years by several writers (Lander, 1936; Erwin, 1939; Lander and Davidson, 1938), and experimental proof of the correctness of the view is given by them. When the bronchus is plugged absorption of the air in its area of distribution takes place and that section of the lung undergoes collapse. Collapse of any extent of lung tissue leads to an increase of the negative intrapleural pressure—that is demonstrated in a striking way when a lobe becomes atelectatic during pneumothorax treatment —and this outward pull, which in a healthy lung is taken up by the air-containing tissues, in the collapsed lung falls upon the bronchi which are immediately subjected to a dilating stress If the collapse is rectified before infection results no permanent damage is done, but if it remains so long that infected secretions collect behind the plug in the bronchus permanent damage to the lung tissues and bronchial walls results. With a plastic plugging agent such as sputum there is a tendency for the plug to liquefy and to be pulled further down the bronchial tree as air absorption proceeds, and finally the fragments come to rest in the finer bronchioles. Our conception of collapse must thus be based on something smaller than the large bronchus. The lobule in some cases may be the unit, and lobular collapse is common in bronchopneumonia. In this we see a reasonable explanation of that

confusing picture, to which I have already referred, of post-pneumonic fibrosis in children, the more fortunate of whom recover while the less fortunate proceed through stages of advanced suppuration and lung tissue destruction to the final stage of fœtid bronchiectasis.

Cystic Disease.—Intimately related to bronchiectasis is the cystic lung. The origin of these cysts is a matter of dispute, but there is no doubt that many are of congenital origin. Generally they are of two types, multiple and solitary, and it is with the first type that I am concerned here. The multiple cysts may involve a lobe, or more than one lobe. They are often associated with bronchiectasis of the usual anatomical types and they may or may not have bronchial communications. In recording a series of 11 cases, Young and Oswald (1937) describe a symptomatology like that of the post-pneumonic fibrosis of childhood with its recurring coughs and febrile colds. The condition in their cases was discovered only on X-ray examination. The consensus of opinion is that both the cystic and bronchiectatic conditions are congenital and the clinical problem is that of the bronchiectatic child.

Abscess.—In this necessarily condensed survey of the field of chronic lung disease it is better to group diseases according to type rather than orthodox classification, and lung abscess follows in natural sequence to bronchiectasis. It is not a disease *sui generis* but is secondary to other conditions. Its diagnosis presents as a rule little difficulty. Its treatment has many problems. I shall not deal here with the multiple abscesses of pyæmia. By lung abscess we mean the solitary abscess, and it has a fairly well-defined ætiology. Many series of cases have been published. Recent writers (Scott-Pinchin and Morlock, 1930, 1935; Young, 1932; Maxwell, 1934; Price Thomas, 1935; Burrell, 1938) agree that the majority of cases follow pneumonia, or sepsis in other parts of the body, or are associated with lung cancer, while a varying percentage follows operations on the mouth or fauces. Before the abscess ruptures the symptoms may be vague, but malaise, chest pain, rigors, fever, and cough may be prominent. When communication with a bronchus is being established hæmoptysis often occurs, and when the pus is coughed up the diagnosis is obvious. The physical signs are never characteristic and it is only after expectoration of the pus that the X-ray shadow shows a fluid level. Lipiodol rarely enters the abscess cavity. Clubbing of the fingers appears early in the course of the disease.

Although the initial diagnosis is straightforward enough the nature of the abscess must be determined, and careful examination by bronchoscopy and radiography is necessary to exclude the possibility of a breaking-down cancer, an impacted foreign body, or old-standing bronchiectasis. The bearing of this on treatment needs no elaboration. Interlobar empyema rarely causes confusion. When it bursts through the lung it does so late in the disease.

In an interesting article Touroff and Neuhof (1941) differentiate between the *putrid and non-putrid types* of abscess. The former is of inhalational origin, is localised, and demands surgical treatment. The latter develops from a "necro-suppurative" pneumonia and very often disappears with conservative treatment. Differentiation of the types demands no elaborate technique of investigation. The human nose served our fathers and still has its part to play at the bedside.

The Solitary Cyst.—I have already referred to the single lung cyst. These cysts may be huge, replace a whole lung, and resemble a pneumothorax (Roberts, 1937-38; Shanks *et al.*, 1938). They are pathological rarities, but the smaller solitary cyst may present a problem in diagnosis, especially when it communicates with a bronchus and infection of its contents has taken place Lipiodol rarely enters the cyst, and the cough and expectoration of purulent material raise the suspicion of lung abscess. Certain points lead to the diagnosis. The patients have rarely any history of preceding acute illness, they are seldom ill when seen, and the sputum is not foul, for no breaking-down of lung tissue has taken place. The X-ray film shows a cavity with a fluid level, situated usually in the lower lobe, with a thin, well-defined wall and no surrounding lung reaction In this respect it differs sharply from an abscess cavity. These cysts may not give rise to symptoms until adult life is reached, and they may remain symptomless unless they establish a bronchial communication

Chronic Pneumonia.—In discussing the diagnosis of tuberculosis of the lungs I referred to the diagnostic criterion of finding tubercle bacilli in the sputum. While tuberculosis is the chief of the chronic inflammatory diseases of the lungs, it has been realised since the days of Laennec that causes other than tuberculosis may operate, and in recent years Scadding (1936, 1939) has drawn attention to the frequency of chronic non-tuberculous lung inflammations. There has been a traditional description of chronic pneumonia in the guise of the fibroid lung which may

be the end-result of several distinct processes and which is often tuberculous or bronchiectatic, or both; but the cases recorded by Scadding in his earlier paper, some of which were investigated pathologically, had, distributed throughout both lungs, foci in all stages of pneumonia, early consolidation, resolving consolidation, organisation and suppuration. The duration of their illness varied from several months to two years, and fever, cough, spit, hæmoptysis and dyspnœa were outstanding symptoms. A clear lymphocytic pleural effusion accompanied one case. The X-ray appearances were very like those of tuberculosis. In his later paper Scadding described four patients, one of whom died, who had illnesses of several weeks' duration, characterised by small foci of pneumonia scattered throughout several lobes. The radiographical appearances resembled tuberculosis, but in the patients who recovered complete resolution took place. He gave to the condition the name of *disseminated focal pneumonia*, his earlier cases being classed as *chronic diffuse broncho-pneumonia*. In a discussion of *chronic localised pneumonia* he makes a division into chronic non-suppurative and chronic suppurative types, and he believes that the latter is responsible for many lung abscesses of obscure origin. This whole group of chronic pneumonias, diffuse and localised, must be differentiated from tuberculosis, and differentiation may be difficult. In the midst of the easy cuts to diagnosis which beset us nowadays the simple features of disease are apt to be overlooked, but we should not forget that the tubercle bacillus is the ultimate cause of tuberculosis, and where the one is there will the other be also Its absence should make us chary of a diagnosis of tuberculosis, but the course of the illness alone may in time determine its nature.

Friedländer bacillus infection causes a pneumonia which is apparently lobar in type but which consists essentially of confluent areas of broncho-pneumonia. Multiple abscess formation results and the mortality of the condition is high. Rarely the disease pursues a chronic course (Belk, 1926; Collins and Kornblum, 1929) and a chronic suppurative pneumonitis results. The symptoms, physical signs, and X-ray appearances may be very like those of tuberculosis, but tubercle bacilli are not present in the sputum and Friedländer's organism can always be recovered from it. Recovery from this stage is rare but it does occasionally take place, and the resemblance to tuberculosis may become even closer. Extensive fibrosis with the persistence of cavities

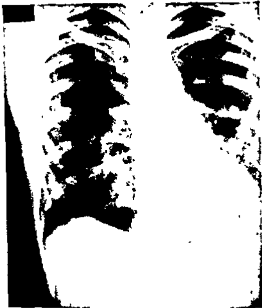


Fig. 1*a*.—Girl aged thirteen. Long-standing history of cough and expectoration. The film shows traction of the heart to the left and the dense shadow of a collapsed lower lobe behind the heart shadow.



Fig. 1*b*.—Lipiodol injection reveals a collapsed, completely bronchiectatic, left lower lobe.



Fi[illegible]



Fig 3a—Man aged forty-one Dense opacity of lower half of right lung partly due to lobar collapse



Fig 3b—Lipiodol injection shows complete blockage of lower lobe bronchus The cause was a bronchial carcinoma



Fig 4—Lymphadenoma in a boy of seven years The film shows huge hilar glandular masses with a shadow in the right upper lobe partly due to lobar collapse



Fig 5—Man aged thirty Parenchymal cancer of left upper lobe confirmed by operation

results, and Collins and Kornblum state that "so closely may these diseases simulate each other that in certain cases neither the clinical nor the roentgenologic evidence serves to make the differentiation." Radiographically the cavities have thinner walls than the tuberculous cavity, but the diagnosis rests essentially on the bacteriological examination of the sputum. In the group of chronic suppurative pneumonias described by Scadding Friedländer bacillus infection was not found.

Tumours.—Tumours of the lung form a large part of the problems of lung disease and may arise from the lung itself, from the mediastinum, or from the tissues of the chest wall. They may be simple or malignant, and they offer a wide field for description and discussion. The *mediastinal* tumours, which include lympho-sarcomata, dermoids, teratomata, fibromata, lipomata, thymus tumours and the substernal thyroid, are essentially space-occupying tumours and their symptoms are those of pressure. Until they reach a size sufficient to produce pressure they may be silent, unless degeneration or infection has arisen. They can be diagnosed with accuracy only by X-ray investigation and, although they may compress the lung, they are not true lung tumours. Similarly those interesting growths of *nerve tissue*, the ganglio-neuro-fibromata, are midline parietal tumours, but they may simulate lung tumours and their site of origin can be proved only by the performance of a diagnostic pneumothorax, which will collapse the lung and leave the tumour attached to the chest wall. Of *pleural* tumours the commonest is the endothelioma, and the outstanding features of its symptomatology are pain and blood-stained pleural effusion. In comparison with growths of the bronchi and lung substance, it is relatively uncommon. Aspiration of the fluid and replacement by air may be necessary to show the tumour radiographically, and inspection with the thoracoscope will reveal its nature or allow removal of a portion for histological examination. I shall refer later to the diagnostic significance of the pleural effusion.

The commonest cause of massive enlargement of glands in the lung roots is *lymphadenoma*, which may give rise to very big tumour masses. The swellings may involve the true lung root glands alone or they may include the retrosternal mediastinal glands, and parenchymatous involvement of the lung is not uncommon. The lung involvement may take the form of radiating strands of lymphatic infiltration, of coarse round nodules which may degenerate to form cavities, of disseminated masses of

irregular size which may resemble tuberculosis, and of massive pneumonic infiltration. Sometimes the root gland and lung involvement are the only evidence of the disease and diagnosis may be very difficult, but usually the chest involvement is part of the general process which presents little difficulty in diagnosis

The hilar gland involvement of the primary tuberculous infection in children has rarely the massive character of lymphadenoma.

Simple tumours of the lung are rare. Those of the bronchi are relatively uncommon, and unless they occlude the bronchus or cause hæmoptysis may give rise to few symptoms. I shall not elaborate their symptomatology, but I wish to refer in more detail to that interesting tumour which is midway between the simple and malignant, the *polypoid adenoma*. An extensive literature on this tumour has grown in recent years, and full descriptions will be found in the writings of Brock (1938), Edwards (1939), Goldman and Stephens (1941), and Foster-Carter (1941). It arises from the bronchial mucous glands and is allied pathologically to the mixed salivary tumours. It is as common in women as in men, and in this respect differs from the bronchial carcinoma. It produces symptoms relatively early in life and the symptoms lack the rapid progress of the bronchial cancer. The tumour is very vascular, and hæmoptysis is frequent and may for a time be the only symptom Cough appears later. The growth in time blocks the bronchus and leads to collapse of the lung in its area of distribution. Sudden collapse may lead to a sudden onset of dyspnœa, but the blockage is usually gradual and for a time before its occurrence the patient may have been aware of a wheeze in that area of the chest. The bronchial blockage brings in its train the usual sequelæ of suppuration and bronchiectasis. Empyema is a late but common complication. The hæmoptysis, fever, and expectoration may lead to a diagnosis of tuberculosis, and unless attention is paid to the bacteriological examination of the sputum that diagnosis may go unchallenged A characteristic of the tumours is that they often grow through the bronchial wall and form large masses outside of the bronchus, and removal of the bronchial portion may leave a large lung mass intact The clinical picture of bronchial obstruction and lung suppuration should always lead to bronchoscopic examination That alone can confirm the diagnosis of a bronchial tumour, but a blocked bronchus can always be demonstrated radiographically by the injection of

lipiodol. Histological examination of the tumour may be very confusing unless the pathologist has been informed of the probable clinical diagnosis. The growth is locally invasive but does not metastasize.

Of the *malignant tumours* of the lung the only one of significance is the *bronchial carcinoma*. These tumours are common and their incidence is on the increase. There is little doubt now that all lung carcinomata are of bronchial origin, and those masses which appear to spring from the mediastinum are main bronchus tumours which have grown from the bronchus into the mediastinum. The main bronchi are the usual site of origin, but growths in the tertiary and terminal bronchi account for the rarer parenchymal and peripheral tumours which lie free in the lung fields. The behaviour of these latter types differs from that of the first or main type, which grows to block the bronchus and infiltrates the lung later by lymphatic permeation Although lung cancer occurs in young people it is essentially a disease of middle or later years, and lung symptoms in an older person should always arouse the suspicion of malignant disease. The symptoms of onset may be quite indeterminate, but a history of an initial attack of so-called influenza is surprisingly common Occasionally a metastasis is the first indication of the primary growth. Distressing and unproductive cough, chest pain, dyspnœa, and the expectoration of blobs of blood come later All are very suggestive of lung malignancy. The later blockage of the bronchus leads to the picture of collapse and lung suppuration. The X-ray film may show a tumour mass or an area of lung collapse, and no investigation is complete which does not include a lipiodol injection. Bronchoscopy should not be delayed and an exploratory thoracotomy may be justifiable particularly in the central types of growth

The *peripheral* and *parenchymal* types of tumour are liable to degenerate and they may very quickly give a clinical and radiographical picture of lung abscess When intact they may be difficult to diagnose, the differential diagnosis being in the first instance from tumours of nerve origin or tumours of the chest wall. The possibility of these solitary masses being metastases should not be overlooked and the hypernephroma and seminoma should be kept in mind. The hydatid cyst may simulate them very closely, and it is not unknown in this country. The solitary unruptured congenital cyst must also be excluded.

Pleural effusions is a common accompaniment of lung cancer

and may be the first presenting sign. The fluid is often blood-stained, a point of diagnostic importance. It may be associated with secondary deposits in the pleura, but more often it is the result of mediastinal lymphatic blockage. In both cases it indicates that the disease is advanced Involvement of the lymphatic system takes place later in the peripheral and parenchymal types than in the main bronchus growth, and rapid assessment of the nature of these tumours is of supreme importance from the point of view of treatment, for they can sometimes be dealt with by surgical removal of the lobe or lung.

An interesting type of malignant lung growth is the *apical bronchogenic carcinoma* to which the name of superior pulmonary sulcus tumour was given by Pancoast (1932). He described the growth as probably arising from embryonal rests in the fifth pharyngeal pouch, but Owen, Hewer and Whitaker (1938), who reviewed the literature in an interesting article which recorded seven cases of their own, show that in the majority of cases the tumours are peripheral bronchogenic carcinomata arising in the lung apex. When the tumour invades the area between the root of the neck and the apex of the lung it involves the cervical sympathetic chain and the brachial plexus, and causes a group of symptoms characterised by motor and sensory disturbances of the shoulder and arm of the affected side, atrophy of the hand muscles, and Horner's syndrome. Symptoms of lung disease may be entirely absent, and in only one of their recorded cases was cough present. The tumours are easily demonstrated radiographically.

Pneumoconioses.—Proliferation of fibrous tissue is the end-result of many pathological lung processes, and an unqualified diagnosis of fibrosis is often a confession of ignorance. The diseases caused by dust stand, however, in a special category. The causal agent is essentially irritant, and lymphatic blockage and the accumulation of the dust in the lung tissues leads to destruction of the alveolar constituents and massive replacement by fibrous tissue. There are many irritant dusts Each has its specific effect, but the most dangerous are those containing soluble *silica*. Inert dusts are insoluble and may cause few effects until big accumulations have taken place in the lung glands and lymphatics. Soft coal dust belongs to this group. It is rare, however, for the worker to inhale one dust only, and in the dangerous silica trades inert dusts are inhaled along with the active silica containing dusts and add their contribution to

the advancing fibrosis. Most pneumoconioses are thus composite, and the lung tissues offer in the words of Cummins (1935) "a kind of palimpsest of the individual's industrial history." The end-result of silicosis is a massive fibrosis on which tuberculosis is often grafted.

The inhalation of *asbestos* fibre particles gives its particular type of fibrosis and the *asbestos body* can always be recovered in the sputum (Wood and Gloyne, 1934; Sparks, 1938). Pathologically and radiologically the fibrosis is less dense and less diffuse than in silicosis, but the symptoms may be just as severe. Tuberculosis supervenes in a smaller proportion of cases.

The outstanding symptom of these trade fibroses is progressive and disabling dyspnœa, and unless tuberculosis supervenes there may be few other symptoms. Diagnosis presents no real problem. The disease is peculiar to its trade, and the radiographical picture, especially of silicosis, is typical. It is perhaps appropriate to recall that silicosis has now been recognised in the coalfields of South Wales (Med. Res. Publ. No. 243, 1942), and its presence in some Scottish coalfields is not unknown.

Syphilis.—Syphilis may give rise to gummata in the lung, and syphilitic stenosis of bronchi is not uncommon Syphilitic fibrosis of the lungs is described but has not been placed on any established pathological basis. At the best such a diagnosis is rarely more than speculative, but I think there is little doubt that syphilis may alter the character of lung tuberculosis by imparting to it a chronic fibrotic character

Fungus Infections.—Of those rarer diseases caused by the group of fungi, I propose to refer to two only, one caused by the moulds and one by the streptothrix class of organism. Both may cause great confusion in diagnosis and both should be kept in mind as diagnostic possibilities

Mycotic infection of the lungs occurs chiefly in agricultural workers and has been described by many writers. The best known in this country is probably Fawcitt (1938), who has described the condition in various grades of agricultural workers The outstanding feature of the illness is progressive dyspnœa, and the condition if untreated may progress to a dense permanent fibrosis. The clinical signs are those of a fine bronchial catarrh, and cough may be associated with purulent spit, hæmoptysis, and fever, all suggestive of lung tuberculosis; but tubercle bacilli are not present in the sputum and the dyspnœa is out of all proportion to the physical signs and is of a severity unusual in

phthisis. The onset of the illness is gradual but the breathlessness is progressive, and that symptom in a farm worker should raise a suspicion of mould infection. The radiographical picture of the established disease may resemble closely the pneumoconioses, and the final picture is that of diffuse dense coalescing areas of fibrosis. Multiple small cavity formation and bronchiectasis sometimes occur. Moulds may be found in the sputum, but that investigation involves many pitfalls and must be carried out by an experienced bacteriologist. The moulds concerned—mucor, aspergillus and penicillium—are all related to mouldy hay, straw, grain, or manure.

The *streptothrix group* of organisms, of which the actinomyces are the main members, may involve the lungs and cause a widespread granulomatous infection which produces symptoms very like those of tuberculosis, and if the upper lobes are involved the picture may be quite indistinguishable from that disease (Shanks *et al.*, *op. cit.*) The disease, however, in time usually involves the pleura and reaches the skin, and the first hint of its nature may be the presence of the characteristic sulphur granules in the pus. Widespread formation of fibrous tissue takes place in the lungs in the later stages, but primarily it is a disease of tissue destruction and may resemble tuberculosis. The persistent absence of tubercle bacilli from the sputum should make us suspicious of that diagnosis, but unless the granules are noticed in the sputum the disease may remain undiagnosed until involvement of the tissues of the chest wall has taken place.

Sarcoidosis.—The conception of Besnier-Boeck's disease, or Sarcoidosis, has been widened in recent years and it is now recognised that the pathological process may attack any part of the reticulo-endothelial tissue system. The lungs may be involved at an early stage in the process and a coarse atypical fibrosis, partly nodular, may result. The condition is usually symptomless (Scott, 1938; Hannesson, 1941) so far as the lungs themselves are concerned, and its true nature may only be recognised by the development of other manifestations of the disease. The presence of cutaneous sarcoids makes the diagnosis obvious, but lung involvement without skin involvement is not uncommon. The illness may simulate chronic miliary tuberculosis and the nodular element in the X-ray film may increase the confusion (Cameron and Dawson, 1942).

Heart Disease.—I may be forgiven for mentioning such an obvious condition as the heart of mitral disease and the pulmonary

symptoms which may accompany it. During the periods of breakdown we are unlikely to misinterpret its significance, but during periods of apparent compensation cough, expectoration, and even hæmoptysis may all be referable to it and the lungs may provide signs which may mislead the unwary.

The Clinical Approach.—In this discussion I have said little of physical signs. They are related to pathological processes which are common to many of the diseases. The infiltration, the liquefaction of tissue, the cavity, and the fibrosis each has its sign, and added to those are often the signs of collapse. They must be interpreted in association with symptoms and co-related with radiographical findings Symptoms overlap from disease to disease but they belong to a fairly restricted group. Cough is of prime importance and sputum has its types, while spitting of blood varies in quantity and character. These symptoms in their varying combinations dominate lung symptomatology and they are worthy of careful bedside observation and appraisal. But there are others. Pain, apart from the pain of pleurisy, is rare in disease of the lung. When present it has its significance, and the patient's story should always be heard. Bronchial asthma is a true disease even if its cause is varied and obscure. The careful observer will not confuse it with the graver forms of respiratory embarrassment. The pleural effusions have a diagnostic significance. The early tuberculous effusion of the young, the blood-stained exudate of the old, and the transudate of the failing heart or degenerating kidney all have their message. Each in its way is a pointer to diagnosis, but we should not forget that a clear lymphocytic effusion may accompany conditions other than tubercle. The age and occupation of the patient should always be considered. The one narrows the field of possibilities. The other may give a clue to the significance of symptoms. The patient himself is worthy of study. His appearance, the state of his nutrition, the presence or absence of respiratory distress, of glandular enlargements, of clubbing of fingers and toes, are all within our field of observation, and a general examination may establish the diagnosis The bedside tests which served the old clinicians can serve us still It is the integration of properly assessed symptoms and properly interpreted physical signs into a complete clinical picture which forms the basis of all diagnosis The art of Medicine remains in our hands, and it is for us to preserve it against the pseudoscientific methods which permeate much of Medicine to-day. The laboratory has its place and we

must utilise its specialised services, but we should retain diagnostic control of our patient and be reasonable in the requests which we make of its workers. The function of the radiologist is growing and diagnosis is often impossible without his aid. He is a colleague to whom we should confess, and with whom we should discuss, our difficulties. He is more than an obliging producer of facile diagnoses. Our debt to the bronchoscopist grows daily, and he, with the radiologist, has played a major part in the advancement of diagnosis of chest disease. What radiology may suggest bronchoscopy can often prove.

I have tried to cover a wide field in a short time, but the field of lung diagnosis is a broad field to till. I have made a plea for clinical observation and the employment of reasoned judgment in diagnosis. I have pled for the art of Medicine. The older among us need no conversion, but the younger will, I hope, take from my remarks the message that he retains the truest perspective in Medicine who utilises to the full the senses and faculties with which Nature has blessed him.

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on both legs and thighs and several smaller similar areas on the arms. There was no purpura and no anæmia. No other signs of deficiency disease were detected clinically and no significant hæmatological abnormality was found. A tentative diagnosis of scurvy was at first made, but the situation, size and appearance of the bruises suggested a traumatic origin. This was subsequently confirmed independently, although the patient continued to deny assault.

Particular care is needed when assessing the value of a previous history of unusual bleeding and, especially, when interpreting the family history, frequently of primary importance in the bleeding diseases, but so often liable to be misleading Thus, for example, of 527 apparently healthy female blood donors appearing for the first time for blood withdrawal, 49 (9·3 per cent) said they bled excessively from small injuries, and 50 (9·5 per cent.) admitted to bruising easily from trivial often unrecognised injuries Of these 99 subjects, 15 (2·9 per cent. of the total) apparently presented both unusual features. Subsequent experience has revealed the potential unreliability of such statements All the above donors have since given blood on one or more occasions without untoward result; in only one was anything unusual noted at the withdrawal, a considerable petechial eruption below and distal to the occluding cuff

An example of a condition in which bleeding may be attributed to abnormal or unusual forms of trauma may be found in the description of the following case .—

CASE 2.—H. S , aged 31, was an apparently healthy laboratory worker with no previous or family history of hæmorrhagic diathesis This subject's blood had repeatedly been examined over a number of years, having frequently been used as an experimental control and to standardise technical methods and apparatus It was further known that his capillary resistance had been for a prolonged period within the usual limits, and the snake venom reaction had been found to be negative on a number of different occasions. Four previous single dental extractions at age 17, 25, 26 and 28 had been accomplished with minimal bleeding, the first under local anaæsthesia. On 22 9 41 a fifth tooth was removed without difficulty under gas and oxygen, and bleeding ceased within one hour Some 4 hours later, however, bleeding recurred and continued for 26 hours in spite of local pressure with gauze, liquor ferri perchloridi and adrenalin. This hæmorrhage, much of which was inevitably swallowed, was sufficient to produce general malaise, nervous irritability, anorexia and nausea Had the circumstances been different, considerable anxiety would doubtless have been occasioned as the result of the continual bleeding which was due in this case, as in many others, to an abnormal

THE VITAMINS IN RELATION TO HÆMORRHAGE

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THE conditions which may lead to the occurrence of bleeding either externally or into the tissues are numerous and, as yet, incompletely understood. It can be said, however, that excessive or abnormal bleeding may be due to excessive trauma, to abnormal or unusual forms of trauma, or to mild, even "physiological" injuries to a vascular system in which the integrity of the processes which normally prevent the occurrence of bleeding is in some way impaired. On this view all forms of bleeding are occasioned by trauma, the word being extended to include the physiological stresses and strains which are involved, for example, in the processes of muscular activity and the maintenance of the erect posture. Hæmorrhage then occurs as the result of a defect in the body's mechanisms for the arrest of bleeding. The expression "spontaneous hæmorrhage" is thus, strictly speaking, a contradiction in terms, and bleeding may be the response of the vascular system to stimulation. This conception, which is represented schematically in Fig. 1, involves a more dynamic view of the hæmostasis mechanisms than is at present customary and emphasises the importance of trauma in the initiation of all forms of hæmorrhage, even those associated with, and characteristic of, the so-called bleeding diseases with certain forms of which this lecture is primarily concerned

Circumstances in which hæmorrhage occurred as the result of excessive trauma are exemplified in the following case history which serves to emphasise the care required in obtaining and *assessing the clinical histories of all cases who present hæmorrhage* as a leading symptom.

CASE 1.—Mrs J McB, aged 32, a housewife. For a week before admission to hospital this patient gave a history of radiating pain

revealed definite pain on passive movement of the legs, especially the right, but, beyond brisk reflexes, little else could at first be made out. More detailed examination, however, revealed numerous ecchymoses

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methods whereby bleeding is prevented break down, and one of the bleeding diseases becomes manifest. Such a latent disturbance will also tend to aggravate or maintain bleeding from other causes, for example, menstruation, and may be revealed or made manifest by surgical operation, accident or injury.

A primary analysis of the mechanism of hæmostasis is presented in Fig. 1. Each part requires perhaps a word of explanation.

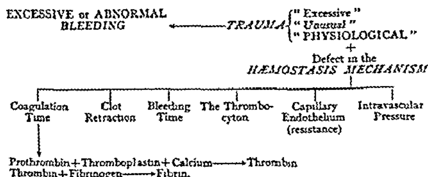
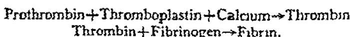


FIG. 1.—A scheme illustrating factors involved in the development of pathological bleeding

The processes of *coagulation* have so far defied complete analysis. It is customary, however, to recognise two associated reactions.



Prothrombin+Thromboplastin+Calcium→Thrombin
Thrombin+Fibrinogen→Fibrin,

but it should be recognised that these expressions represent biological and not chemical reactions, and that they therefore do not possess any quantitative significance. A sample of human blood, for example, contains a large excess of prothrombin over and above that required for the coagulation of all the fibrinogen contained in it, and the amount of thrombin produced as a result of the former reaction is many times greater than that used up in the second. Furthermore, the rate of conversion of prothrombin into thrombin varies in different species even when due allowance is made for differences in the prothrombin content of the plasma (Warner, Brinkhous and Smith, 1939), and quite large qualitative variations in the ability of fibrinogen to form fibrin have been noted (Herbert, 1941).

Clot formation has not been extensively investigated, and

or unusual form of trauma resulting in the opening of vascular channels of sufficient size properly to require ligature. Although in such circumstances a material degree of trauma to the gums may be found on examination and the bleeding controlled by suture, in others there is little to indicate that unusual damage has been done.

A more dramatic example of hæmorrhage following unusual trauma is the following case:—

CASE 3.—W. A., an engineer, aged 53, attended hospital with general paralysis of the insane. He was given a course of treatment with a pentavalent arsenic preparation and bismuth and improved considerably as a result. After having received 22·0 g. of the arsenic preparation and 1·8 g. bismuth metal he reported at the hospital two days after his weekly injection, complaining of feeling a little out of sorts and with a stiff right leg and a limp. On examination it was found that an extensive hæmatoma involved the whole of the right gluteal region which was tense and tender. The discoloration extended to above the level of the iliac crests and downwards as far as the right knee. The following day the hæmatoma was even more extensive, the whole of the leg and foot being involved. There was extreme tenderness in the gluteal region and down the back of the thigh. In view of the extent of the lesion, the patient's incapacity and the general symptoms of which he complained, he was admitted to hospital A full hæmatological examination was undertaken without, however, revealing any cause for the bleeding. In particular the bleeding time, coagulation time and thrombocyte count were within normal limits, the snake venom reaction was negative and the capillary resistance had not been unduly low during treatment, nor was it so immediately before the hæmatoma developed There was no evidence of scurvy. It was established that the last injection had been given on the right side and that the patient had varicose veins It was finally concluded that the bleeding was not a manifestation of intolerance, but was due to the accidental rupture of a vessel at the time of injection. No interruption was made in the patient's treatment, and he has subsequently tolerated 20 g of tryparsamide and 1·8 g bismuth without untoward effect.

Although it is convenient to recognise a number of different processes, all of which are directed towards the arrest of bleeding, it is certainly incorrect to visualise these functions as distinct. The parts into which the hæmostasis mechanism may be divided are to be regarded rather as interrelated processes in a complicated and ever-changing biological pattern, the complete understanding of which still eludes us. The efficiency of the hæmostasis mechanism may become impaired as the result of a defect in one or more of its parts, or it may be, because of a disturbed relationship between the various interdependent reactions that the usual

difference was well illustrated in the case of hæmophilia mentioned above. Shortly before he was to have left hospital this patient sustained a scratch 1½ ins. long on the back of the right forearm. The amount of bleeding was insignificant and no dressing was required. On the same day, as a result of trauma insufficient almost to be noticed, a large and completely disabling hæmarthrosis developed in the right knee joint. It is generally held that in the control of bleeding from deep wounds in which relatively large vessels may be severed, the contraction of these vessels plays the major part, whereas in superficial injuries the thrombocytes play the chief rôle by adhering to the injured endothelial surfaces, so forming a mechanical plug. This process, which may well have a chemotatic basis, is different from true coagulation and, indeed, its hæmostatic efficiency may remain unimpaired even when, as in hæmophilia, the process of true coagulation is so defective that the coagulation time occupies many hours. It is well to note, however, that Macfarlane (1941) has produced evidence that even with small superficial injuries the structure and contractility of capillaries play a major part in the arrest of bleeding. We have recently observed a correlation between the bleeding time and the capillary resistance; subjects with a high capillary resistance tend to have a short bleeding time, whereas, when the fragility of the capillary walls is increased, the bleeding time is found to be relatively prolonged (see, for example, Figs. 2, 4 and 8). These observations likewise point to the capillaries as a potentially important factor in the control of hæmorrhage from superficial wounds

The *thrombocyton* is a term which, on analogy with the "erythron" of Boycott (1929), may be conveniently used to include not only the absolute number of thrombocytes in the peripheral blood but also their functional efficiency (agglutinating potency and fragility), believed by some to be impaired in hæmophilia The word also includes the production of thrombocytes in the bone marrow which may be defective as the result of a specific maturation arrest, of a toxic effect on the bone marrow in general or the thrombocytopoietic tissue in particular, or of a replacement of the megakaryocytes by leukopoietic or neoplastic cells

Certain evidence suggests that the integrity of *capillary function* is one of the most important, if not the most important, factor in the arrest of bleeding, at any rate from superficial wounds. The properties of the capillaries which appear to be

comparatively little is known either about this interesting and important process or about the related phenomenon—spontaneous fibrinolysis. At least two properties of the clot may be distinguished—its friability and its ability to retract from the walls of the confining vessel, expressing serum as it does so It is usually considered that these two functions are related, so that a clot which does not retract in a normal way is found to be unusually fragile, a phenomenon which is characteristically found in association with thrombocytopenia. However, in a case of *hæmophilia in a youth of eighteen recently investigated* and found to have a thrombocyte count within normal limits, the clot appeared to retract normally, but was characterised by very marked friability.

The *bleeding time* is a complex function about which much remains to be discovered. In the present state of our knowledge it is well to remember, and relevant to point out, that estimations of the bleeding time answer one question and one question only, namely, "How long does the patient bleed when a small superficial cut is made?" The precise significance of the phrase "small superficial cut" has not apparently been defined. An attempt was made to investigate this point in a case of hæmophilia in a youth aged nineteen, in whom the bleeding time was measured after successive punctures of gradually increasing depth. The results set forth in Table I would appear to indicate that a puncture between 1·5 and 5 mm in depth may be expected to be satisfactory in determining the bleeding time.

TABLE I

Relation between Bleeding Time and Depth of Puncture in a Male, aged 19, *with Hæmophilia*

Depth of Puncture Mms	Bleeding Time Mins	Coagulation Time, Mins
1·0	?2	?
1 5	3	20
2 0	3	18
4 0	3½	15
5 0	3½	18
6 0	over 24 hrs	20

It is clear that the mechanisms to which arrest of bleeding from a small superficial puncture are chiefly due are different from those which control hæmorrhage from a deeper wound. This

increased intracapillary pressure is achieved by means of venous occlusion; in the latter a measurable negative pressure is allowed to act upon the capillary walls through the skin, and their resistance or fragility is assessed in terms of the least negative pressure required to produce a single ruptured capillary (petechia) in the area under examination. The method devised has already been outlined in some detail (Scarborough, 1941, (1)). The capillary resistance is usually determined in three separate areas on the volar surface of the forearm and the results in each area are recorded separately in the charts which follow. There is no evidence that the resistance of the capillaries in the deeper tissues and organs bears any relation to that of the surface vessels. It should also be stated that this technique assesses capillary resistance and not capillary permeability, there being at present no experimental information bearing upon the relationship, if any, between these two properties of the capillary wall

Thrombocytopenic Purpura and Vitamins A, C, and P

Although it is extremely unlikely that all the many problems presented by the bleeding diseases have a direct relationship to the vitamins, it is clear that an increased understanding of the physiological efforts of the latter substances has contributed to our knowledge of a group of diseases about which much still remains to be discovered. The first problem to which we may usefully direct our attention is that of idiopathic thrombocytopenic purpura. Arising from the knowledge that ascorbic acid controls the bleeding which is so characteristic a feature of scurvy, and following the observation of Wolbach (1926, etc) and more recently of Hunt (1941) that this hæmorrhage is associated with, and probably due to, alterations in intercellular matrix in and around the smaller blood vessels, came the idea that the hæmorrhage of thrombocytopenic purpura might also benefit from this form of treatment. This suggestion acquired more force when considered in relation to the fact that the latter condition resembles many (but not all) cases of scurvy in being associated with a low capillary resistance

In 1937 Vaughan, reviewing the literature on the treatment of thrombocytopenic purpura with ascorbic acid, reached the conclusion that the chance of favourably influencing the course of this condition by means of ascorbic acid was approximately 1 in 3. In addition to the 21 cases referred to by Vaughan, we have

important in this respect are their morphology, their power of contracting rapidly and of maintaining the contracted state, and the resistance of their walls to injury (capillary resistance or fragility).

The *pressure within the vessels* whose continuity has been interrupted by trauma may be thought to be a factor in the production of bleeding. The development of increased intracapillary pressure, for example by venous occlusion, prolongs the bleeding time in the tissues distal to the obstruction (for example see Case 8, Fig. 6, and Case 9, Fig. 7), and the shortness of the bleeding time in cases of shock is well known. It is probable, however, that in the latter condition factors other than the low intravascular pressure are involved.

It is impossible within the confines of a single lecture to adduce sufficient evidence fully to support many of the statements which may be made, and accordingly it should be understood that the cases later to be described are selected and not necessarily the only examples which illustrate the relevant points. A proper understanding of the charts will not be complete without reference to the methods of investigation employed.

Methods

The bleeding time was determined by a modification of the method of Duke or by Ivy's method. The latter is referred to in more detail on page 53. In all cases a puncture 2·5 mm. deep was made.

Thrombocytes were enumerated by the indirect method from stained films of citrated blood. There are, it is true, certain cogent criticisms of this technique, but in our experience it works fairly well in practice and it undoubtedly possesses certain advantages of its own.

The icteric and prothrombin indices were determined by the standard methods of Meulengracht and Quick respectively. An extract of dried brain was the source of thromboplastin in all estimations of prothrombin time which are expressed throughout in the form of a prothrombin index (Illingworth, 1939).

The capillary resistance, or fragility, is the property of the walls of the surface capillaries to withstand alterations in pressure applied to them, either from within as in the so-called positive pressure principle, or from without by suction, as in methods based upon the negative pressure principle. In the former an

Her previous health had, on the whole, been good, but she had once been treated for "anæmia." On two previous occasions (aged 38 and 40) she had noticed petechiæ on her legs, and she has tended to bruise very easily for as long as she can remember. On eight occasions during the last four years she had fairly severe epistaxis. The menopause at age 40 was passed without excessive loss, but menstruation, though regular, had always been heavy. The dietary history appeared satisfactory in all respects and there was no family history of bleeding.

On examination, the patient was well nourished but had evidently lost weight recently. There was mild anæmia. A massive eruption of fairly widely scattered petechiæ, varying in size from less than a millimetre to several millimetres, was present on both legs below the knee. Three small hæmorrhages were found in the mouth and the ecchymoses, referred to above, were present in the right upper arm. There was no external bleeding. No enlargement of the liver or spleen could be detected.

Hæmatological examination gave the following typical result:—R b c. 3·75 M. Hb 80 per cent. Sahli (12·8 g /100 ml.). W.b.c. 4200. No abnormal cells in films. Bleeding time (Duke) 12 minutes. Coagulation time 5 minutes. Clot retraction defective Thrombocytes under 50,000 p mm.[3] Capillary resistance low. Snake venom reaction, +ve. B.P. 100/70. Diagnosis; Idiopathic thrombocytopenic purpura.

The subsequent progress of this case is represented in Fig. 2, in which graphic records of the bleeding time, thrombocyte count, and capillary resistance are shown. Energetic intravenous treatment with vitamin C and later with a preparation of vitamin P, whose potency had already been established by control observations on another subject, failed to produce any significant effect on the bleeding time, thrombocyte count or capillary resistance, and further petechial hæmorrhage of minor degree appeared from time to time. Throughout this period the patient was taking a diet containing a high proportion of fresh fruit and vegetables. The record also shows that splenectomy produced a favourable response in bleeding time, thrombocyte count and capillary resistance, and immediately controlled the bleeding. Three years later this patient had resumed her work in apparently good health with a bleeding time of 3 minutes, a thrombocyte count of 180,000 per mm.[3] and an increased capillary resistance.

A certain amount of experimental evidence exists that vitamin A is concerned in some way in the proper functioning of the thrombocyton, at any rate, in certain animals. Thrombocytopenia was noted in vitamin A deficient rats as long ago as 1923 by Cramer and Drew, and although some workers have considered the reduction not marked or constant enough to constitute a specific lesion, the finding has been repeatedly confirmed. Recently Lorentz (1936, 1938) has reported that

found ten reports in the literature, six being favourable and four unfavourable. The subject would therefore seem to merit further investigation, and the following 3 cases bear upon this point. It is important in this connection to recognise that evidence exists that in certain circumstances ascorbic acid taken by mouth is more effective when derived from natural sources and consumed

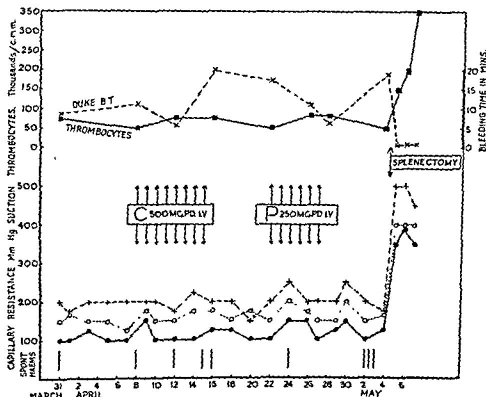


Fig. 2.—The effect of ascorbic acid, vitamin P and splenectomy on the bleeding time, thrombocyte count and capillary resistance in a female aged 43 with idiopathic thrombocytopenic purpura. The incidence of petechial bleeding is indicated by vertical lines in the lower part of the chart. The bleeding time was determined by Duke's method. Mg. P.D. I.V. = milligrams per day intravenously.

in the form of fruit, than when given as the synthetic material (Elmby and Warburg, 1937).

Case 4 (Fig. 2).—Miss C. R., aged 43, shopkeeper. Some three weeks before her admission to hospital this patient complained of dull aching pain in the calves of both legs. This was shortly followed by a massive petechial eruption, by epistaxis and by the development of two ecchymoses about 2 inches in diameter on the right upper arm. At the same time the patient felt unduly tired and unable to do her work.

Her previous health had, on the whole, been good, but she had once been treated for "anæmia." On two previous occasions (aged 38 and 40) she had noticed petechiæ on her legs, and she has tended to bruise very easily for as long as she can remember. On eight occasions during the last four years she had fairly severe epistaxis. The menopause at age 40 was passed without excessive loss, but menstruation, though regular, had always been heavy. The dietary history appeared satisfactory in all respects and there was no family history of bleeding.

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vitamin A is capable of increasing the thrombocyte count in both guinea-pigs and children, but he was unable to find any favourable effect of large doses of vitamin A in a single case of Werlhof's disease in a girl aged nine.

CASE 5 (Fig. 3). Miss H. L, aged 59, a housekeeper, had been apparently in good health until four days before her admission to hospital, when she felt a little giddy. The same evening bleeding occurred from the right ear and continued until she came to hospital On the following day she bled from her mouth, and by the evening an extensive petechial eruption had developed on the lower limbs. On the day of admission blood was noticed for the first time in the stool. The only previous history of unusual bleeding was at the menopause, twenty years before the present illness, when she had four or five similar attacks which, she thinks, were more severe than the present one. There was no family history of bleeding A dietary history revealed a deficiency of fresh fruit and vegetables in the diet, though the patient took potatoes.

On examination the patient was well nourished There was no anæmia. Both upper and lower limbs were almost covered with small discrete petechial spots of a size not exceeding 1 mm. There were several larger purpuric spots on the tongue, two larger hæmorrhagic areas in the soft palate, and there was bleeding from the nose and from the right ear, both of which ceased spontaneously within twenty-four hours of admission to hospital.

No enlargement of the liver or spleen could be detected.

On the basis of full hæmatological investigation a diagnosis of idiopathic thrombocytopenic purpura was made.

Fig. 3 illustrates the progress of the case and the response to treatment In the upper part of the chart are records of the capillary resistance (in a single area) and the thrombocyte count, and in the lower part an attempt has been made to assess the amount of subcutaneous hæmorrhage present from day to day. "E" represents the development of ecchymoses in response to which a prompt but temporary elevation of capillary resistance occurred—a phenomenon to which attention has already been drawn (Scarborough, 1941 (2)). A diet consisting largely of fresh vegetable foods and fruit, together with three eggs and two pints of milk per day, supplemented by the oral administration of large doses of ascorbic acid failed apparently to have a favourable effect upon the course of the disease. Kugelmass (1932) drew attention to the value of dietary treatment in exerting a favourable effect on a defective hæmostasis mechanism, although in what manner fat, especially lipoid, and protein exerted their effect was

not made clear. The findings of Kugelmass have, however, not found general acceptance and are afforded no support by the cases we have investigated. Large daily doses of a pure preparation of vitamin A, over ten times the normal daily requirement given by mouth over a period of fourteen days, likewise failed to control bleeding or influence the thrombocyte count. In two other

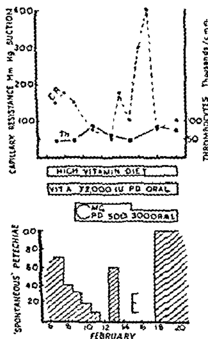


FIG 3—The effect of a high vitamin diet together with ascorbic acid and vitamin A on the capillary resistance, thrombocyte count and incidence and amount of subcutaneous bleeding in a female aged 59 with idiopathic thrombocytopenic purpura. The development of subcutaneous bleeding is assessed quantitatively in the lower part of the chart E = ecchymoses, and represents a greater suffusion of blood than is represented by the figure 100 P D = per day.

cases vitamin A given parenterally in single doses of 100,000 to 250,000 I U has likewise proved ineffective.

The bleeding tendency in this patient after a prolonged stay in hospital gradually became less prominent, and the patient was ultimately allowed to return home, although she continued to bruise very easily and to develop mild petechial eruptions from time to time For the last three years she has been able to do light housework but still occasionally has purpura Her thrombocyte count has never been found to be above 75,000 per mm ³ since she first came under our care

Between 1935 and 1939, Schiff and Hirschberger successfully treated cases of thrombocytopenia in children with preparations of vitamin A. They later obtained data which they interpreted as showing that the substance, active in increasing the thrombocyte count, and stated to be present in certain (not all) preparations of vitamin A, was not, in fact, this vitamin but a fat-soluble substance

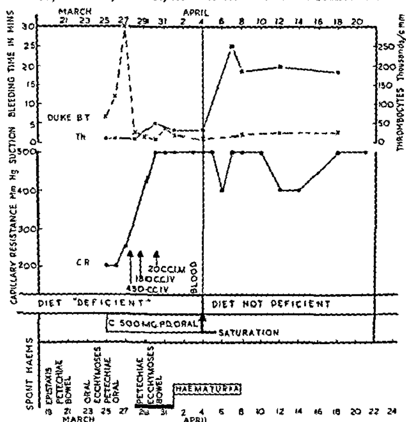


FIG 4.—A record of the bleeding time, thrombocyte count, capillary resistance and development of hæmorrhage in a female aged 17 with idiopathic thrombocytopenic purpura For explanation of therapy and interpretation see text The lower part of the chart indicates site and occurrence of bleeding I V. = intravenously. I.M. = intramuscularly

distinct from it. They designated this substance vitamin T. The nature of this material is quite unknown ; it is said to be present in relatively large amount in the yolk of eggs. So far as we know, further evidence in support of the existence of such a vitamin is lacking. The following case history is, therefore, of interest .—

CASE 6 (Fig. 4). Miss H F, aged 17, was admitted to hospital as an emergency with a complaint of hæmoptysis of a month's duration,

and of hæmorrhagic spots in the mouth and in the lips, face and chest, together with intermittent epistaxis for five days.

For three or four months prior to her admission the patient had noticed that she had been more easily tired than usual and had complained of constant anorexia. For two months she had had amenorrhœa, and two months ago consulted her doctor on account of a persistent cough associated with a slight hæmoptysis on three occasions. Five days before admission, during a paroxysm of coughing, she developed epistaxis and, the following morning, a petechial eruption on her lips, face, chest and legs. She was able to go about that day feeling very weak, but fainted on her return home from the doctor's.

There was no previous or family history of bleeding.

Dietary History—The patient lived alone with her father and did the catering and cooking for the household. She, herself, never took meat or eggs, but drank at least a pint of milk a day. She took potatoes and vegetables freely and had fruit, usually an orange, every day.

On examination the patient was clearly very ill with a swinging temperature, low volume tachycardia, and a rapid respiratory rate. Her colour was pale (Hb 42 per cent.) and her expression distressed. There were clots of blood at the angles of her mouth and nose. An ecchymosis about the size of half-a-crown was present on the right cheek and another involved the right tonsil and surrounding area. Petechiæ were present in the soft and hard palates, in the tongue and buccal mucosa, over the cheeks, neck, chest, and both upper and lower limbs.

The stools contained altered blood and the urine very large numbers of red cells She later developed severe hæmaturia. The liver was not enlarged, but the spleen could just be palpated below the left costal margin.

On the basis of a full hæmatological examination a diagnosis of idiopathic thrombocytopenic purpura was made

Fig. 4 is a record of the relevant findings in this case. From above downwards are represented records of bleeding time, thrombocyte count, capillary resistance, therapy, and nature and occurrence of bleeding The chart is complicated and is, no doubt, capable of a number of different interpretations. Saturation with ascorbic acid was first undertaken, but before this could be accomplished deterioration in the patient's condition demanded transfusion. In view of our failure to determine any favourable effect of ascorbic acid in 15 cases of thrombocytopenic purpura, we feel justified in attributing no therapeutic credit to it in this case also. In response to transfusion of fresh blood, or possibly as the result of massive bleeding into the renal tract, the capillary

resistance rose markedly, the bleeding time fell to within normal limits, but the thrombocyte count remained under 50,000 per mm.^{3} On 4th April the diet, from which eggs had until this time been rigorously excluded, was altered to contain four eggs a day. Three days later the thrombocyte count was found to be 250,000 per mm.^{3}, and this improvement was maintained, the patient making an uninterrupted recovery. It is possible in the light of Schiff and Hirschberger's work to attribute the improvement to some substance in the eggs, for there is a clear history of the patient having taken no eggs for many years. It is certainly also possible that the dramatic effect should be described to a late response to transfusion, possibly in association with ascorbic acid. It is probable that the effect is a spontaneous recovery not directly attributable to the therapeutic measures employed. However, when a rare disease is found in association with a most unusual dietary habit, it is permissible to suggest a causal relationship, since the possibility of such an association occurring by chance may be described as remote. When the rare disease is apparently cured by correction of the unusual dietary habit, in this case the giving of a food hitherto lacking from the diet, then the possibility of there being a causal relationship between the two would appear to be strengthened.

Our own experience with 15 cases of idiopathic thrombocytopenic purpura has been that ascorbic acid administered either by mouth or intravenously is of no value in increasing the thrombocyte count, nor does it increase capillary resistance. Vitamin A either by mouth and parenterally is likewise ineffective. Preparations of vitamin P are without obvious therapeutic effect, and a diet containing a high proportion of foods rich in all three vitamins has also proved unsuccessful. Recently both ascorbic acid and a preparation of vitamin P have been injected directly into the sternal marrow in a single case of idiopathic thrombocytopenic purpura, but apparently without any clinical benefit and certainly without favourable effect upon either the bleeding time or the capillary resistance.

The Bleeding Tendency in Jaundice. Vitamins D and K

The relationship of the vitamins to the control of the bleeding tendency in jaundiced patients which may become manifest especially after operation is a much more promising subject, and one in which important advances have recently been made.

It would be a mistake to imagine, however, that the position has now been completely clarified.

In 1934 Dam drew attention to a bleeding disease in chickens which developed, or could be produced, as the result of a dietary deficiency. The condition, which was later found by Dam, Schonheyder and Tage-Hansen (1936) to be due to a coagulation defect occasioned by a lack of prothrombin in the plasma, has now been described in many birds and laboratory animals It is due to the deficiency in the diet of a fat-soluble substance designated vitamin K, though this term is now used to include a group of substances with similar physiological properties. Such a deficiency occurs, if at all, only very rarely in man as the result of a deficient diet (Kark and Lozner, 1939; Scarborough, 1940 (1)). It has been shown that the bacterial flora of the alimentary canal is able to produce vitamin K which is evidently formed in amounts sufficient to protect the organism against such a dietary deficiency. A somewhat similar condition has been described in cattle as the result of their eating spoiled sweet-clover hay (Roderick, 1931), but it is now known that the syndrome which develops in these circumstances, although likewise associated with low plasma prothrombin levels, is due to the presence in the hay of dicoumarin, *i.e* 3 : 3′-methylene-bis (4-hydroxycoumarin), (Stahmann, Huebner and Link, 1941) The marked interference with blood coagulation produced by this compound is apparently not resolved by vitamin K It is possible that dicoumarin may be useful in delaying coagulation in man in those conditions in which heparin is at present employed, but certain evidence suggests that it should be employed with great care and only under the most carefully controlled conditions.

The discovery of Dam was immediately taken up by clinical workers in the hope that it might solve the difficulty of detecting those cases with jaundice which might be expected to bleed after operation and so terminate the controversy which had been going on since 1795 as to the reason for this phenomenon. As a result of the pioneer work of Butt, Snell and Osterberg (1938) at the Mayo Clinic, of Dam and Glavind (1938) in Denmark and of Illingworth (1939) in this country, it is now established that a prothrombin deficiency may exist in jaundice not as the result of a deficiency of vitamin K in the diet, but because, in the relative absence of bile from the intestine, fats, and therefore fat-soluble substances, in particular vitamin K, are not efficiently absorbed.

The following case is an example of this phenomenon :—

CASE 7 (Fig. 5). A. B., a grocer, aged 56, had been complaining of flatulent dyspepsia with anorexia and loss of weight associated with gradually progressive jaundice of some six weeks' duration. On investigation the jaundice was found to be obstructive in type, and the final diagnosis, confirmed at subsequent operation, was carcinoma of the head of the pancreas.

Shortly after the patient's admission to hospital the prothrombin

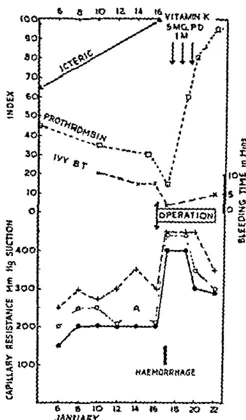


FIG 5.—The effect of surgical operation on the plasma prothrombin level, bleeding time and capillary resistance in a male aged 56 with carcinoma of the head of the pancreas and obstructive jaundice Hæmorrhage occurred on 17th January.

index was found to be 45 per cent of normal and the icterus index 65 (Fig. 5) Cholecystostomy was performed twelve days later when the prothrombin index had fallen to 30 per cent and the icterus index had risen to 125. Twenty-four hours after operation the prothrombin index had fallen to 15 per cent, and secondary hæmorrhage occurred from the wound. This was promptly controlled by administration of a synthetic vitamin K analogue (2-methyl-1 . 4-naphthoquinone) by intramuscular injection and the prothrombin index increased rapidly to within normal

limits. Before operation the bleeding time was slightly prolonged, but was found to be normal within twenty-four hours of the operation at a time when hæmorrhage was occurring. The capillary resistance showed a marked increase following operation and was unusually high when bleeding occurred. The post-operative fall in the plasma prothrombin level occurs most commonly within twenty-four to seventy-two hours after operation, but may not develop until the sixteenth day. It may be prevented by the injection of a vitamin K analogue or by the oral administration of bile salts.

In other conditions associated with defective fat absorption (*e.g.* sprue and other forms of steatorrhœa), low plasma prothrombin values may also be found. When the defective fat absorption is due to the absence of bile salts from the alimentary tract, as in jaundice, then the bleeding tendency may be corrected by the oral administration of vitamin K together with bile salt, or a synthetic analogue may be given by intramuscular injection. Very recently water-soluble preparations possessing vitamin K potency in high degree have become available, *e.g.* 1 : 4-naphthaquinone-3-disodium succinate (Synkavite) and 4-amino-2-methyl-1-naphthol hydrochloride (Kayvisyn). These preparations, which can also be given intravenously, do not require bile salt for their absorption.

It is important to remember that the action of vitamin K in increasing the plasma prothrombin and so correcting the coagulation defect is dependent on adequate hepatic function (Pohle and Stewart, 1940; Bollman, Butt and Snell, 1940). Following Dam and Glavind (1938) a number of workers, including Kark and Souter (1940, 1941), have observed that low plasma prothrombin levels can be found in disorders of the liver without jaundice, in cirrhosis, for example, and that in these conditions, as also in certain jaundiced patients, administration of vitamin K, even parenterally, does not increase the plasma prothrombin. In our own experience, however, although values below the lower limit of normal may not infrequently be found in such cases, figures for the prothrombin index low enough to occasion anxiety as to the early possibility of hæmorrhage occurring have never been observed

The success which has attended the use of preparations of vitamin K in controlling the bleeding tendency of obstructive jaundice has naturally led to its administration in other bleeding diseases. There is, however, no evidence that vitamin K is effective in conditions not characterised by hypo-prothrombinæmia, and,

in fact, the only bleeding disease for which the vitamin has by general consent proved of great value is the hæmorrhagic diathesis of the new-born. Although doubt still exists as to the exact mechanism of the hypo-prothrombinæmia in these cases, and although different observers have noted its onset at different times during the first week after birth, there is abundant evidence that a hypo-prothrombinæmia exists during the second, third and fourth days after birth, during which time a latent tendency to bleed is present and may become manifest. It is important, however, in assessing the possible value of vitamin K preparations in the treatment of such cases, to distinguish between the " physiological " icterus with low plasma prothrombin and other causes of neonatal jaundice such, for example, as the condition called icterus gravis neonatorum or erythroblastosis. Evidence is accumulating to show that the latter is due to intravascular hæmolysis in the infant's vessels as a result of a reaction between the Rh antigen of the infant's cells and an anti-Rh agglutinin transferred through the placenta from the maternal blood. It is of interest to note, however, that a case has been reported of icterus gravis neonatorum with erythroblastosis which was going downhill in spite of repeated intramuscular injections of whole blood, but in which definite improvement occurred within twelve hours following the administration of vitamin K and bile salts by mouth. The baby ultimately recovered (Mayman, 1940). It may be as well to point out in this connection that Sanford, Shmigelsky and Chapin (1942), in an investigation which included observations on 1693 new-born infants, found that although the plasma prothrombin values of infants given vitamin K, and of infants whose mother had received vitamin K before delivery, were well above those of normal infants throughout the neonatal period, the frequency of hæmorrhagic manifestations—conjunctival, vaginal, petechial, cerebral and umbilical hæmorrhage, melæna and cephalhæmatoma—were just as frequent in a group of 711 infants who had received vitamin K as in the group which had not The mortality rate in the two groups was the same .

While determinations of the prothrombin index (or prothrombin time) may frequently give information as to the possibility of hæmorrhage occurring after operation in jaundiced subjects, it is noteworthy that determinations of the patient's coagulation time by the older techniques (Sabrazé, Wright, Lee and White) have in general proved unsatisfactory for the detection of the latent bleeding tendency in obstructive jaundice. In

contrast, determinations of the bleeding time have proved of greater value, especially when these are made by the method devised by Ivy and his associates (1935). In this procedure the bleeding time is determined during venous occlusion, a pressure of 40 mm. Hg. being maintained throughout the determination in a sphygmomanometer cuff applied to the upper arm. In a series of 810 miscellaneous cases, Ivy and his co-workers found that a large number of patients with jaundice showed a prolonged Ivy bleeding time, and that the length of the bleeding time had an important prognostic significance. They made the further

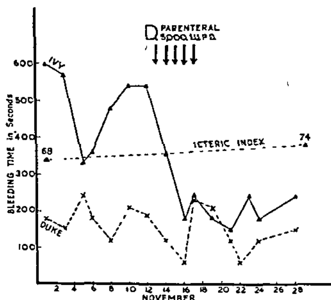


FIG. 6 —The effect of injection of a vitamin D preparation on the bleeding time in a male aged 58 with carcinoma of the stomach, metastatic involvement of the liver and jaundice. I U P.D = international units per day.

observation that the bleeding time could be reduced in "almost all" cases by the administration of preparations of vitamin D together with bile salts. These observations have been confirmed in their essentials by other workers. The following is a case in point .—

CASE 8 (Fig. 6). J. McK., a gardener, aged 58, had complained for eight weeks of dyspepsia, anorexia, loss of weight and gradually increasing jaundice which, on investigation, proved to be obstructive in type. The liver was palpable some 2½ inches below the costal margin, firm, with a regular surface, and not tender on examination. There was

evidence of congestion at the base of the right lung, but nothing else of significance was detected on physical examination. Radiographic examination of the alimentary tract revealed a localised filling defect at the pyloric end of the stomach. Fractional gastric analysis showed achlorhydria with a fasting juice having a blood-stained deposit and containing charcoal. A diagnosis of carcinoma of the stomach with metastatic involvement of the liver was made. Operation was not advised and the patient was allowed to return home.

Fig. 6 includes a record of the patient's bleeding time determined by the methods of Ivy and of Duke. It shows that initially a normal result by the Duke method was associated with an abnormal value by the Ivy technique (upper limit of normal 240 seconds), a relationship to which attention was drawn by Ivy and his co-workers. Parenteral administration of vitamin D in the form of ostelin in doses of 5000 I.U. per day for five days reduced the Ivy bleeding time to normal. This effect did not appear to be associated with any clinical improvement. The icterus index increased during the investigation.

The mechanism whereby vitamin D exerts this effect is unknown. It is apparently the view of Ivy that variations in fragility of the clot afford an explanation for the phenomenon, but there is little direct evidence to support this view. Boyce (1940) has related the bleeding tendency in jaundice to the "serum volume index" (*i.e.* the amount of serum expressed by the clot at the end of four hours at room temperature), which is evidently a quantitative expression of clot retraction. Very recently Ivy and his co-workers (1941) have been able to show that administration of a preparation of vitamin D (viosterol) does not increase the plasma prothrombin level. Our own observations indicate that the reduction in the bleeding time following vitamin D is associated with an increase in capillary resistance, and suggest, therefore, that the difference is to be related to this function of the capillary wall. While fully recognising the part played by a low prothrombin level in the circumstances already alluded to, we are inclined to believe that alterations in the capillaries play a large part in the hæmorrhagic tendency in many cases of jaundice. A somewhat confusing situation is further complicated by the work of Dr A. I. S. Macpherson in this hospital He found (1941) a prolonged bleeding time in hæmorrhagic disease of the new-born which was reduced to within normal limits by administration of vitamin K.*

* The author is responsible for drawing these conclusions from Dr Macpherson's published results.

The Vitamins in Relation to Hæmorrhage

The existence of a hæmorrhagic tendency in certain cases of liver disease not accompanied, by clinical jaundice has been recognised for many years. Although the condition has somewhat unfortunately been designated "pseudo-hæmophilia hepatica" it has no relation to true hæmophilia. The mechanism whereby the phenomenon is produced has not been satisfactorily elucidated, but it is possible that a number of defects acting together is responsible, rather than the disturbance of a single function. Although it is true that the prothrombin index may often be found to be below normal in this condition (values between 50 and 75 per cent. of normal are not infrequently found), we have never found results low enough to justify our attributing the hæmorrhagic tendency to this factor alone. The possibility, however, must be recognised that more detailed investigation of the process of coagulation in such cases may yet yield significant results. It is now generally admitted that the condition is not due to a functional defect in, or an absolute deficiency of, plasma fibrinogen, which is, in point of fact, often increased above the normal level of 0·2-0·4 g. per 100 ml. It likewise cannot be explained on the basis of quantitative or qualitative alterations in serum calcium. The coagulation time is usually normal whether determined by one of the capillary methods or by the method of Lee and White which employs venous blood. The bleeding time is, however, often prolonged, especially if determined by the Ivy method—a point to which attention was drawn by McNealy, Shapiro and Melnick (1935). In association with the prolonged bleeding time an unusually low capillary resistance is, in our experience, invariably present and, in fact, a positive tourniquet (Hess) test can often be obtained. In this connection it is interesting to recall the observations of Patek, Post and Victor (1940) who have confirmed certain earlier work emphasising the occurrence of vascular abnormalities in relation to hepatic cirrhosis, and of Epstein (1939), who by means of infra-red photography was able to demonstrate morphological abnormalities in the superficial vascular network which were not detectable by other means. Finally, one may recall the observations of Györgi, Poling and Goldblatt (1941), of Daft, Sebrell and Lillie (1941) and of Webster (1942), who have obtained evidence in animals that certain forms of hepatitis may be the result of dietary deficiency. Urabe (1940) has been able to demonstrate hepatic dysfunction in pellagra, and Warner, Spies and Owen (1941) have observed four cases of nutritional deficiency with low

plasma prothrombin levels which were not increased by oral administration of vitamin K. The experimental work of Rich and Hamilton (1940) and of Spellberg and Keeton (1940), as well as the clinical experience of Connor (1939) and of Patek (1937), support the view that a relationship exists between nutritional deficiency and hepatic cirrhosis.

Because the explanation for the bleeding tendency in chronic hepatitis has not been fully elucidated, efforts directed towards

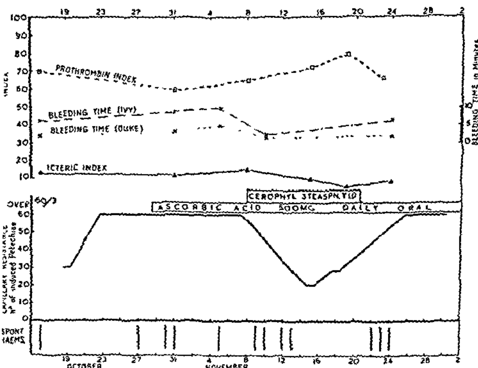


FIG. 7.—A record of prothrombin and icteric indices, bleeding time, capillary resistance (by a positive pressure method) and occurrence of petechial bleeding in a male aged 61 with hepatic cirrhosis.

its control have met with little success. The following two cases are of interest in this connection :—

CASE 9 (Fig. 7).—R. B., aged 61, a blacksmith. Following a burn on his right leg produced thirty-five years ago by pure carbolic acid, the patient had been dressing the area with 1 : 40 carbolic for twenty-five years! As a result of this treatment the leg had to be amputated eight years before his present illness began. Signs of "chronic carbolic poisoning" were said to have been present at that time. After the operation the patient was well until four months before he came to

hospital, when his left leg became very painful and œdematous. About a month after this he developed a gradually progressive ascites. Three weeks before his admission to hospital the patient began to be troubled with mucous diarrhœa, together with frequent and intractable vomiting. No blood was ever noticed in the stool or vomit, neither of which had ever been unduly dark in colour. Exertion dyspnœa was the only other important symptom.

His previous health had been good. He had pneumonia on one occasion and was formerly a heavy drinker. There was no previous or family history of bleeding.

On examination the patient was found to be stout and plethoric, with vascular patterns prominent on both cheeks. There was gross ascites and œdema of the left leg and right thigh (the right leg having been amputated below the knee). There was no clinical jaundice. After paracentesis abdominis the liver was found to be enlarged to 2 inches below the right costal margin, the surface being nodular and the edge firm and irregular. The spleen was not palpable.

Diagnosis.—Cirrhosis of the liver.

This man had never had a hæmatemesis and did not suffer from piles. There was no recent history of epistaxis. In the fifth week of his stay in hospital a fine petechial eruption occurred on both legs. Fresh crops of petechiæ appeared thereafter at intervals of from a few days to a week.

R.b.c. 4·98 M [illegible] mbocytes 280,000. F [illegible] No abnormal cells. [illegible] time (capillary blood) 4 minutes. Prothrombin index 70 per cent. Icteric index 12. Indirect van den Bergh reaction, faintly +ve. Capillary resistance —very low. Hess test +ve. Lævulose tolerance impaired. Urobilinuria.

The subsequent progress of this case is illustrated in Fig. 7, which illustrates from above downwards records of the prothrombin index, bleeding time by Ivy's method, bleeding time by the method of Duke, icteric index, therapy, capillary resistance, and occurrence of spontaneous petechial bleeding. It will be seen in the first place that the occurrence of bleeding cannot be related solely to the level of the prothrombin index, since this was never found to fall below 60 per cent.; it is generally agreed that bleeding does not occur from this cause operating alone until the prothrombin index falls below 30 per cent. The view that the impaired prothrombin level may have contributed to the manifest bleeding tendency is, however, tenable. This case also demonstrates how the Ivy bleeding time may be abnormal, although normal values are given by the Duke method (*cf.* Case 8, Fig. 6). The capillary resistance has here been assessed by a

positive pressure method in which the resistance is measured in terms of the number of petechiæ enumerated in a standard area on the front of the forearm under standard conditions of time and pressure (60 mm. Hg. occluding pressure acting for 3 minutes). In contrast to the other graphs, therefore, an increase in resistance (decreased fragility) is here represented by a fall in the chart and, conversely, a decrease in resistance (more fragile capillaries) by a rise, since the more fragile the capillaries are the larger the number which rupture as a result of the standard conditions of the test. During the earlier part of the investigation the capillary resistance remained low and the Ivy bleeding time increased. Large doses of ascorbic acid for a prolonged period did not affect either of these functions; it did not control the bleeding nor did it appear to produce any beneficial clinical effect. Ascorbic acid was administered in this evidently wasteful manner in connection with a parallel investigation for which large amounts of urine with a relatively high ascorbic acid concentration were required. On 8th November the administration of cerophyl was begun. Cerophyl was one of the early preparations of vitamin K. It was prepared from alfalfa grass and contained besides vitamin K many other substances, including, for example, vitamins A, B_1, and C (Illingworth, 1939). This material did not restore the prothrombin index to normal levels as it is frequently capable of doing (see Illingworth, 1939), presumably because of impaired hepatic function In association with its administration, however, the capillary resistance was increased and the Ivy bleeding time definitely reduced It appeared also that the bleeding tendency was improved, though this interpretation is open to question. When cerophyl was withdrawn the capillary resistance increased, the bleeding time became prolonged and petechial bleeding recurred. Subsequent work has shown that vitamin K analogues are without effect upon capillary resistance, and we are therefore inclined to attribute the results to some other material present in cerophyl. The patient upon whom these investigations were made died later from broncho-pneumonia; unfortunately no autopsy was performed.

Case 10 (Fig 8).—Mrs J C, aged 51, a housewife About three weeks before her admission to hospital this patient first noticed her complexion slightly yellow. This jaundice became gradually deeper. Her appetite had been very poor and her bowels increasingly constipated She had progressively lost weight More recently she had been troubled by severe vomiting, especially after food, by distressing gastric flatulence

and by epigastric discomfort and distension. Two or three days before she came to hospital she noticed that several bruises had appeared in various parts of the body although she was in bed at that time.

On examination the patient was obviously jaundiced, the jaundice being of the obstructive type. She had evidently lost weight but was still quite well nourished. Nine ecchymoses ranging in size from a threepenny-piece to over half-a-crown were found together with petechial spots on the chest and upper arms. The lower edge of the liver was palpable 1½ inches below the right costal margin. The organ was firm and tender and no irregularities could be detected. The spleen did not appear to be enlarged

Diagnosis.—After further investigation a tentative diagnosis of carcinoma of the head of the pancreas was made, but at operation this was modified to interstitial pancreatitis, a diagnosis which was felt to be supported by the findings at a second operation ten weeks later An associated hepatitis was also present.

R b c. 3·90 M. Hb 82 per cent. Sahli (13·1 g./100 ml). Thrombocytes 240,000. W.b c. 9200. No abnormal cells. Icteric index 82. Van den Bergh, direct positive. Prothrombin index 70 per cent. Coagulation time (capillary blood) 4 minutes. Bleeding time (Duke) 5 minutes. Urobilinuria +++.

This patient has been under more or less continuous observation for over nine months. Fig. 8 represents a record of part of the findings. It commences some five weeks after the patient was admitted to hospital and eighteen days after a cholecystostomy had been performed. At the beginning of this record the icteric index was 33, but the jaundice gradually diminished, the index being 14 on 29th December. Throughout the whole of this period of the investigation a certain amount of bile was leaking externally, but the greater part appeared to be reaching the small intestine, and the patient was taking bile salt daily in the form of 2 g. of sodium taurocholate. The prothrombin index, initially 60 per cent, increased to 92 per cent. following parenteral administration of vitamin K, but fell subsequently to a level of some 50 to 80 per cent. The capillary resistance (negative pressure method) fell gradually during the early part of the investigations, during which period the bleeding time (Ivy method) was increased above the normal. Neither of these functions was affected by parenteral administration of vitamin K The administration of coramine (N-diethyl nicotinamide) by the mouth at a time when the capillary resistance had fallen to a low level resulted in a marked increase in capillary resistance associated with a reduction in the Ivy bleeding time to within the limits of normal. In the later part of the investigation the

positive pressure method in which the resistance is measured in terms of the number of petechiæ enumerated in a standard area on the front of the forearm under standard conditions of time and pressure (60 mm. Hg. occluding pressure acting for 3 minutes). In contrast to the other graphs, therefore, an increase in resistance (decreased fragility) is here represented by a fall in the chart and, conversely, a decrease in resistance (more fragile capillaries) by a rise, since the more fragile the capillaries are the larger the number which rupture as a result of the standard conditions of the test. During the earlier part of the investigation the capillary resistance remained low and the Ivy bleeding time increased. Large doses of ascorbic acid for a prolonged period did not affect either of these functions, it did not control the bleeding nor did it appear to produce any beneficial clinical effect. Ascorbic acid was administered in this evidently wasteful manner in connection with a parallel investigation for which large amounts of urine with a relatively high ascorbic acid concentration were required. On 8th November the administration of cerophyl was begun Cerophyl was one of the early preparations of vitamin K It was prepared from alfalfa grass and contained besides vitamin K many other substances, including, for example, vitamins A, B_1, and C (Illingworth, 1939). This material did not restore the prothrombin index to normal levels as it is frequently capable of doing (see Illingworth, 1939), presumably because of impaired hepatic function. In association with its administration, however, the capillary resistance was increased and the Ivy bleeding time definitely reduced It appeared also that the bleeding tendency was improved, though this interpretation is open to question When cerophyl was withdrawn the capillary resistance increased, the bleeding time became prolonged and petechial bleeding recurred. Subsequent work has shown that vitamin K analogues are without effect upon capillary resistance, and we are therefore inclined to attribute the results to some other material present in cerophyl The patient upon whom these investigations were made died later from broncho-pneumonia, unfortunately no autopsy was performed

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capillary resistance was allowed to fall to a point at which spontaneous bleeding occurred (24th, 26th and 27th January) At this time the bleeding time (Ivy method) had risen to 12 minutes Five hundred c.c. orange juice daily for three days was now given, and this apparently resulted in an increase in capillary resistance and a relative reduction in bleeding time, although on the basis of this single experiment such a conclusion can only be tentative. A second operation for closure of the fistula performed on 3rd February was followed immediately by a marked increase in capillary resistance and a reduction in bleeding time. At this operation (cholecystenterostomy) a small piece of liver was removed for examination; it is not without interest that this was considered by the pathologist (Dr R. F. Ogilvie) to show the features "of associated fatty degeneration and focal necrosis of the liver—the types of changes which occur during, and are responsible for, the production of common cirrhosis" Some nine months later this patient is still under investigation. She feels very tired from time to time, is easily exhausted, and requires to take iron almost continuously to prevent the development of hypochromic anæmia Her capillary resistance remains low and her bleeding time by Ivy's method prolonged.

It is evident that, although the discovery of vitamin K and the elucidation of its mode of action has led to an increased understanding of the processes underlying the bleeding tendency in hepatic disease, especially those forms of it associated with jaundice, and has unquestionably placed a valuable therapeutic agent in our hands, all this work has not served completely to explain the mechanism of the hæmorrhage which occurs with certain other forms of liver pathology in which the development of jaundice is not an outstanding feature. It is to be hoped that the increase in our knowledge of the former condition, the part played in its development by lowered plasma prothrombin levels and the effect of vitamin K preparation in its treatment, will stimulate interest in, and investigation into, the hæmorrhagic tendency which is found in the latter.

Scurvy and Vitamin P Deficiency

It is familiar knowledge that scurvy is characterised by hæmorrhage and that this hæmorrhage is readily controlled by ascorbic acid. It is widely held, indeed the statement will be found in textbooks, that in scurvy the capillaries become unusually

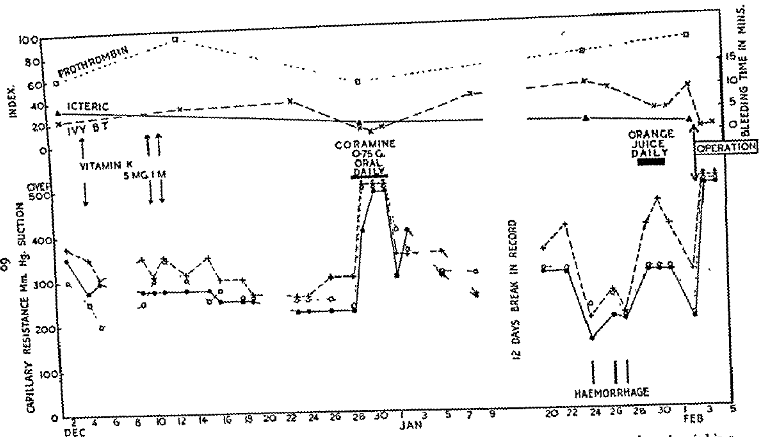


Fig 8.—A chart of the prothrombin and icteric indices, Ivy bleeding time and capillary resistance determined over a prolonged period in a female aged 51 with chronic pancreatitis and hepatitis. The effects of administration of vitamin K, coramine, orange juice and surgical operation are illustrated Vertical lines below the chart indicate subcutaneous bleeding.

present in citrus fruits and in fresh vegetable foods which is capable of elevating the capillary resistance in subjects in whom an undue capillary fragility has been found, or has been experimentally produced, as the result of an absence of such foods from the diet (Scarborough, 1939). This material was designated vitamin P by Szent-Györgyi and his co-workers in 1936 Active extracts possessing vitamin P activity and free from ascorbic acid can be extracted from fruits and their juices, but the precise chemical nature of the vitamin is not at present known. Statements that vitamin P is identical with the flavanone hesperidin should be accepted with reserve; extracts many times more potent, weight for weight, than hesperidin have been prepared from black currants and tested in guinea-pigs (Bacharach and Coates, 1942) and in man (Scarborough, unpublished observations).

Arising out of these observations it is interesting to enquire whether a syndrome can occur, or may be produced, as the result of a specific deficiency of vitamin P. It is possible to think of hæmorrhage occurring not as the result of any abnormality in the blood, but on account of an excessive fragility of the capillary walls which are readily ruptured by mild degrees of trauma altogether insufficient to damage more resistant vessels. Such a conception affords an attractive explanation of the so-called vascular types of purpura, but at present awaits experimental foundation. It has in fact been possible as the result of experimental feeding to produce petechial bleeding in two subjects who had been receiving relatively large supplements of ascorbic acid daily for prolonged periods (Scarborough, 1940), and a similar condition has since been observed to occur spontaneously This syndrome is characterised by petechial bleeding, by pain across the shoulders and in the legs, by lassitude and undue fatigue and by low capillary resistance, slightly prolonged bleeding time and low serum calcium It is cured by the administration of preparations of vitamin P, but not by ascorbic acid. The following case represents an example of the condition

CASE 11 (Fig. 9)—J G, aged 71, was a brewer's lorryman who had been under our care two years previously with scurvy He had taken alcohol to excess for many years. On the present occasion he again presented the typical manifestations of this disease He complained of mild dyspnœa on exertion, and of lassitude and undue fatigue On examination there was some œdema of the feet and ankles. There was a large ecchymosis involving almost the whole of the posterior part of the

fragile (low capillary resistance), so that a positive tourniquet or Hess test characterises this disease. Further, it is commonly believed that since an adequate intake of ascorbic acid is an important factor in increasing or maintaining the capillary resistance at a so-called normal level, the state of an individual's nutrition, or the general nutritional level of a sample of the population, in respect of ascorbic acid may be assessed by observations on the capillary resistance There is, however, a large and increasing number of reports in the literature which do not support this view. In this connection it is well to recall that such authorities as Hess, and before him Ohnell, have written that the response to the tourniquet test is an unreliable guide to the diagnosis of scurvy, or to determining the presence of the pre-scorbutic state, since negative as well as positive responses are frequently found in these conditions. We have recently found that the subcutaneous or intramuscular injection of blood, or the extravascular suffusion of blood into the tissues, is followed by a prompt and marked elevation of capillary resistance which may be maintained for several days (Scarborough, 1941 (2)). This phenomenon, which has been observed repeatedly both in normal and in scorbutic subjects, is no doubt the explanation for the conflicting results so frequently found in scurvy. Thus in only about one-third of a series of 45 cases of scurvy investigated during the last six years was a low capillary resistance observed at the time of admission to hospital, the remaining two-thirds giving values equal to, or higher than, those found in the general population. Furthermore, it may be observed in a case of scurvy that the capillary resistance, initially high following the occurrence of bleeding into the tissues, will fall gradually to rise again rapidly after a second hæmorrhage.

Even if it could be shown that a low capillary resistance and/or a positive tourniquet (Hess) test was invariably found in scurvy, it would not necessarily follow, having regard to the fact that scurvy is almost invariably a multiple deficiency state, that this was a specific effect of ascorbic acid lack. Before such a statement can be made it is necessary to show that the administration of ascorbic acid, preferably by mouth, can reverse the result of the test It is precisely this experiment which it is so difficult satisfactorily to perform *We have not in point of fact* been able to show that the administration of ascorbic acid either by mouth or parenterally will increase a low capillary resistance. There is, however, a substance, or more probably a group of substances,

right leg below the knee, and others behind the left ankle and below the left knee. The tissues were firm and tender on pressure. Petechial hæmorrhages were also present in the anterior aspects of both legs below the knees. Mild œdema of both feet and ankles was present with perifollicular keratosis involving the medial aspects of both thighs and

made :—R.b c. 5·2 M. Hb 94 per cent. Sahli (15 g./100 ml). W.b.c. 8000. No abnormal cells. Retics. 2·5 per cent. Coagulation time (capillary blood) 5 minutes. Bleeding time (Duke) 7 minutes. Thrombocytes 210,000. Capillary resistance low. Plasma ascorbic acid 0·1 mg./100 ml. Serum Ca. 8·6 mg./100 ml.

The patient was given a "vitamin-free" diet on which he was maintained throughout the investigation. After an initial control period, during which the patient improved symptomatically and the œdema disappeared, ascorbic acid was given in doses of 500 mg per day by mouth, saturation occurring after 8 gm. had been taken. The daily dose of ascorbic acid was then reduced to 100 mg. Following the administration of ascorbic acid the large ecchymoses rapidly disappeared but the petechial hæmorrhages were readily seen as long as a week after the larger bruised areas had resolved. They subsequently slowly faded without showing the colour changes so characteristically seen during absorption of the ecchymoses

A record of the subsequent progress of the case in respect of capillary resistance and development of petechial bleeding is available in Fig. 9, which begins on the day of saturation with ascorbic acid (18th February). The capillary resistance remained low in spite of the administration of ascorbic acid, but no further hæmorrhage occurred until the evening of 14th March, when the patient was allowed to sit in a chair beside his bed for twenty minutes. He complained of a dull aching pain in both legs, and a widespread fine petechial eruption developed over the anterior aspects of both legs below the knee. A similar phenomenon occurred six days later Following the parenteral administration of a *water-soluble vitamin P preparation which elevated the* capillary resistance (in a single area) the patient was allowed up for an hour. No petechial bleeding occurred, but two days later, at a time when the capillary resistance had fallen again, further hæmorrhage developed when the patient was allowed up. Hesperidin was then administered daily by mouth ; the capillary resistance increased and the patient was able to be up without

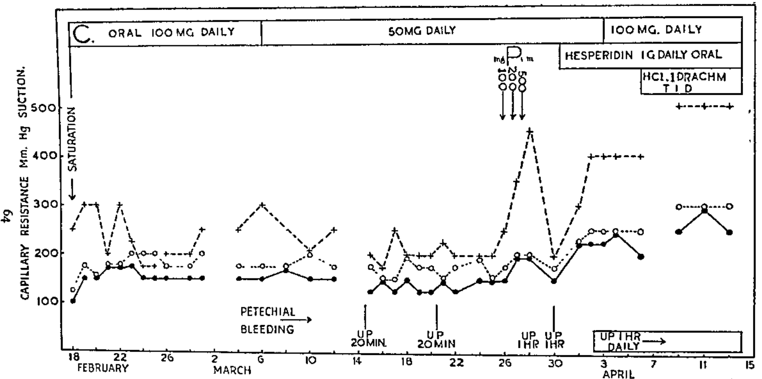


Fig 9—Vitamin P deficiency in a man aged 71 recently cured of scurvy by administration of synthetic ascorbic acid. The chart shows that ascorbic acid did not increase the capillary resistance, which remained at a low level until vitamin P was given. The times at which petechial bleeding occurred are indicated by the vertical lines.

Acknowledgments

It would not be proper to conclude this account of investigations into the place which the vitamins may occupy in the study of hæmorrhagic tendencies and diseases without recording the debt which the author owes to the physicians and surgeons of the Edinburgh Royal Infirmary for their co-operation in providing clinical material and facilities for investigation It is a pleasure also to acknowledge the invaluable assistance afforded by the Sisters of the wards in which observations were made, and to recognise their unremitting care in controlling the many small variables which may so easily prejudice the success of clinical investigations Such facilities are indispensable to the successful prosecution of research in clinical medicine.

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further petechial bleeding. The increase in capillary resistance following the administration of preparations of vitamin P in this case was unusually small: it appeared to be greater during the administration of hydrochloric acid. On 15th March, when the capillary resistance was low and petechial bleeding was occurring, the bleeding time was 12 minutes (Ivy method) and the serum calcium 8·4 mg. per 100 ml.

These observations lend support to the results of investigations already reported (1940), that two forms of hæmorrhage may develop as the result of nutritional deficiency in man. One form is due to ascorbic acid deficiency and is arrested at once by administration of this vitamin. The hæmorrhagic areas are large, involving mainly the deeper tissues, and the typical colour changes are seen during resolution and absorption. Lesions of the mouth and gums are frequently associated and should be regarded as belonging to the syndrome. The other type is characterised by petechial bleeding in superficial tissues and is resolved by the administration of preparations of vitamin P. Resolution appears to occur relatively more slowly and without the typical colour changes. A slightly prolonged bleeding time (Duke and Ivy methods) and a low serum calcium have been consistently found. No associated clinical lesions in other tissues or organs have so far been detected. The former of these nutritional hæmorrhagic states is not necessarily associated with a low capillary resistance; the latter always is. Since, so far as is at present known, vitamins C and P occur together in natural sources, it is to be expected that clinical signs of deficiency of both vitamins will often be associated in a single case. By the use of synthetic materials or purified extracts it is possible, however, to distinguish between them. Evidence has been obtained which leads to the opinion that the syndrome of vitamin P deficiency may exist alone when certain special circumstances condition an increased requirement for, or abnormal utilisation of, this vitamin

It is interesting to consider in the light of these findings whether preparations of vitamin P may be of value in the treatment of certain forms of vascular purpura in which a low capillary resistance would appear to be the chief, if not the only, abnormal finding. Although it is still impossible to make any definite statement on this point, a limited amount of evidence suggests that this vitamin may have a place in the treatment of certain forms of vascular (non-thrombocytopenic) purpura (*e.g.* Scarborough, 1942)

THE PROTECTIVE DIET

By RUTH PYBUS

Sister Dietitian, Royal Infirmary, Edinburgh

I HAVE chosen the Protective Diet for my subject this afternoon, because I think that this aspect of Dietetics is most likely to be overlooked by the medical and nursing professions. We are often so busy telling our patients what they must not eat because they are ill, that we may fail to tell them what they should eat in order to keep well. In acute illnesses of short duration the question of calories, protein, vitamins and minerals may be of little moment, and I think we tend to overfeed the acutely-ill patient. But when a diet has to be followed for many weeks or months, or even for a lifetime, it is essential that it should be adequate in all respects. Quite apart from the dietetic treatment of disease, the doctor may be called upon to give advice about the feeding of healthy individuals in the school, hospital, industrial canteen, the Forces, or in the home. No matter in what branch of work a doctor or a nurse is engaged, he or she should be able to plan a good protective diet both for the treatment and prevention of disease, and by "protective" I do not mean merely a diet which is rich in vitamins, but one which is adequate also in calories, protein, minerals and water.

It is true that an adequate diet is only one consideration in the maintenance of health, but it is probably of greater significance than any other single factor This was well illustrated some years ago in a North of England town, when slum-dwellers were evacuated to a new housing area. Better health was expected from improved surroundings, and great was the consternation when the new living conditions resulted in an increase in the sickness and mortality rates. The explanation seemed to lie in the fact that in the new housing area the weekly rent was a few shillings more, and investigation revealed that this sum was in most cases deducted from the food budget. These few shillings represented the difference between a diet which was just good enough to prevent the most obvious symptoms of malnutrition and one which resulted in a state of positive ill-health.

Poverty is without doubt the greatest cause of malnutrition,

Read 17th June 1943

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pittance who is the most frequent sufferer from scurvy and other manifestations of gross dietary deficiencies; but I know some single women who could afford an adequate diet yet are too lazy to prepare it. They get into the habit of living on tea and buns, they do not trouble to wash a vegetable, and some of them do not even draw their meat or cheese rations.

There is really little excuse for the poor standard of cooking and the complete ignorance of food values which exist in so many homes to-day. Cookery is taught to some extent in most schools in this country, but it is often the stupidest pupils who are encouraged to specialise in domestic subjects. The position seems far from satisfactory, for the Secretary of State for Scotland remarked some weeks ago that 26 per cent of the girls passing out from secondary schools had had no classes in Domestic Science. It is the youth of the country who are most worth while teaching about cookery and nutrition, and it is to be hoped that these subjects will be made compulsory in all schools, and that they will be well to the fore in the youth organisations which are now being formed in all parts of the country

The Ministry of Food is doing a great deal to educate the general public, but the trouble is that it is difficult to reach the people who need this education most. The women who come to cookery demonstrations, or who listen-in to "The Kitchen Front," are usually those who are already good cooks

Doctors, District Nurses and Public Health Visitors have a unique opportunity for teaching the simple facts of nutrition when they visit the people in their homes. But if we expect them to impart this information we must make sure that they themselves are given adequate teaching in practical dietetics

HOSPITAL FEEDING —Many physicians are curiously apathetic about nutrition. Doctors are sometimes interested in the therapeutic aspects of dietetics, but they may pay little attention to the general standard of feeding in their hospitals. If this were not so, old-established hospitals would not still be using the same dietary scales which were drawn up some half-century ago, when, except for protein, food was looked upon as a mere palatable fuel, and the virtues of vitamins and minerals were unsuspected. Some hospitals are now aiming at a very high standard of feeding, but it must be admitted that the routine diet in many cases is a poor example of the type of food we most want our patients to eat when they return home. We might reasonably expect that, if we could plan and cook our hospital

and even in peace-time, in millions of homes in every country in the world, it is frankly impossible to afford a diet which will give a maximum degree of health, vigour and resistance to disease. It is well known that, before the war, about one-third of the population in Great Britain was living on a diet below the standard which we know to be necessary to health. It will be interesting to find what recent dietary surveys reveal, but there is undoubtedly less poverty and unemployment since the war. This can be vouched for by the Almoners' and Out Patient Departments of our hospitals. We are told that at the end of the war we are likely to emerge a healthier and a better fed nation than we were at the beginning. From recent health statistics this would seem to be possible, but I do not think it is necessarily true unless we can avoid certain pitfalls. The greatest improvement may be expected from the wealthiest and the poorest members of the community, for the rich can no longer overeat to any marked extent, and much has been done to safeguard the interests of the poor.

The Government has subsidised and controlled the price of essential foods. There are better money allowances, free and cheap milk for mothers and young children, and more and better school dinners Millions of cheap meals are served daily in British restaurants and industrial canteens, and a great deal is being done to improve the nutritional value of these meals. Moreover, the protective value of the diet has been improved by the introduction of the National loaf and the compulsory addition of vitamins A and D to margarine. Besides, some people are eating vegetables who never ate them before. In spite of these advantages, it is still within the lowest income group that we are most likely to find a deficiency of structure-building and other protective foods, for it is the poor who cannot afford the more expensive unrationed protein foods. It is they who go short of fresh vegetables when these are scarce and expensive.

After taking thousands of diet histories in our Out Patient Department, I am convinced that poverty does play a very real part in malnutrition, but it is also true that ignorance, laziness and food prejudices are sometimes to blame It is not only in the poorest homes that dietary errors are to be found Careless buying, bad cooking, and a total ignorance of food values can prove almost as disastrous as an inadequate income.

Undoubtedly it is the man or woman who lives alone on a mere

vitamins A and C. Hence the drive to grow more carrots, green vegetables and potatoes, and to encourage the full use of the dried milk, dried egg and cheese rations, the addition of calcium to national bread, and vitamins A and D to margarine. Admittedly certain dietary changes have been introduced in order to conserve shipping space, but I think the nation can be proud that, in spite of a world war, or should we say because of a world war, for the first time in history a national food and agricultural policy has been based upon the nutritional needs of the people. An attempt is being made also to persuade the nation to eat such protective foods as are available.

In propaganda about diet, one must not of course over-emphasise the scientific aspect of nutrition. A meal will not appeal just because it is said to be rich in vitamins. It must, at the same time, be palatable and good to look at. By saying too much about calcium, iron or vitamins, we may prejudice people against eating the very foods we most want them to take. Some girls have refused vegetables because they said they could "taste the iron in them." I have known women, with a smattering of dietetic knowledge, object to milk because they feared the calcium it contains would cause constipation, clots in the blood, or render the arteries brittle. One woman, who had snoozed through most of a lecture on diet, remarked at the end that "she never had held with brown bread anyway, for she knew it contained them vitamin bees, and, from the way it went mouldy, she suspected it was full of other insects too!"

CANTEEN COOKING.—Probably the best way to make people like the foods they ought to eat is to serve them attractively and cheaply, at the school dinner, canteen or hostel, and also to improve the standard of cooking in the home. The unappetising mush which is served as cabbage in so many restaurants and institutions is largely responsible for the frequent dislike for greens. In some factory canteens it has been found worth while to charge nothing for raw vegetables at first and to serve them in small quantities in addition to the ordinary dinner. Later, a taste for salads may develop, and these can then form a substantial part of the meal with the addition of some protein food such as cheese or fatty fish, or small amounts of meat.

Recent research has thrown much light on the best methods of preserving vitamins and minerals in the preparation of vegetables in large-scale cookery. This scientific knowledge is of immense value, though it is often difficult to put into practice.

diets in the light of the newer knowledge of nutrition, we might achieve the most rapid return to health of the greatest number of patients, and promote an increased resistance to infection both in the case of patients and of staff. It is true that a patient usually thrives in hospital, and that the food provided is in many instances better than that in his own home, but his condition might be even more satisfactory if his supply of fresh fruit, butter, eggs and tomatoes was assured, instead of depending, as it so often does, upon the generosity of his friends.

Vegetables are poorly represented in most hospital patients' menus. They are lacking in variety, they are overcooked, and little or no provision is made for the patient on light diet who cannot take the fibrous cabbage which is usually supplied.

In most hospitals a good milk supply and a daily serving of meat or fish prevent any marked lack of first-class protein or of calcium; but in case of illness the requirement for first-class protein may be greatly increased owing to inability to take bulky carbohydrate foods, and in order to rebuild tissue which may have been lost during a debilitating illness. Therefore, in addition to the meat or fish at dinner, a second serving of protein should be available for breakfast, and if possible for the tea or supper meal.

In every hospital diet which I have examined, vitamins A and D and C have been noticeably deficient, and this has been more so since the war, owing to the absence of fruit and the curtailing of fat

Before the war, vitamin B_1 was moderately deficient, and iron was often lacking, but, owing to the introduction of the National loaf, these deficiencies have been made good to a great extent, except in the case of patients eating very little bread. Before the war, white bread was used almost exclusively in many hospitals.

National Food Policy.—The defects which are found in hospital dietaries are also noticeable in the nation's diet as a whole, indeed in war-time the protein, calcium and calories are often less satisfactory at home than in the hospital. These defects are not just the result of a war-time food supply, for pre-war dietary surveys revealed that calcium and vitamins A and C never reached a satisfactory level except in the highest income group. This is also true regarding riboflavine and nicotinic acid. The national food policy has been planned with a view to making good these deficiencies, especially with regard to calcium and

Nevertheless quite finely shredded cabbage is still a very good source of ascorbic acid.

If cooked vegetable is left over from the previous day it must of course be used up, but some should be added to raw vegetable salads, as reheating destroys much of the vitamin C. Reheated potatoes and other vegetables are of course useful in other respects.

SCHOOL MEALS.—In most institutions and restaurants it should be possible to cook green vegetables and potatoes in relays, and not to keep them hot for more than a short time, but serious difficulties arise in the case of school dinners which may be cooked at a central kitchen and then transported to the different schools. The meal may contain a fair amount of vitamin C when it leaves the kitchen, but it may contain none by the time it reaches the child. The best solution of the vitamin C problem in this case would seem to be that the food should be cooked at the individual schools. Even so it is desirable that children should be encouraged to eat a certain amount of raw vegetables when citrous fruits are not available. Raw spring cabbages are twice as good as oranges as a source of ascorbic acid, and they are very much cheaper; but it must be admitted that oranges can be eaten in much larger amounts than raw cabbage.

Neither cooked nor raw vegetables are popular in most school feeding centres, but the results of some recent investigations in Hertfordshire schools would suggest that raw vegetables are preferred to cooked. Observations were made at the school feeding-centres, and in addition other children were asked to write an essay expressing themselves freely regarding their likes and dislikes for different vegetables served in their homes. Some of the objections to cooked vegetables were that "they are slimy" or "mushy," or that "they just taste of salt and water." This would seem to be a fairly good description of the vegetable products of the average British cook!

It would, of course, be possible to provide the vitamin C requirement in the form of pure ascorbic acid at the cost of about one penny per day. This is sometimes necessary, but it is always a pity to have to rely on pills and capsules to ensure an adequate supply of vitamins and (except in the case of cod-liver oil) the healthy child should not have to resort to the chemist's shop. Ascorbic acid contains just ascorbic acid—nothing else. Green vegetables contain vitamins A, B_1, B_2, C, P and E, and

I hear from kitchen supervisors in canteens, school-feeding centres, and hospitals, that they are having sleepless nights trying to keep pace with the laboratory findings. Certainly, the elusive behaviour and the disappearing trick of vitamin C is enough to give any cook a nightmare! The vegetables may not be fresh when they are delivered, or they may be badly bruised; or, owing to shortage of labour, they may have to be prepared the day before they are to be eaten. All these factors cause some destruction of vitamin C, and this loss is aggravated by the seepage of ascorbic acid into the cooking water and by prolonged cooking, especially at temperatures below boiling-point. Vitamin C is more stable in an acid than in an alkaline medium, but it is good news that the small amount of bicarbonate of soda, sometimes used to preserve the colour when cooking green vegetables, causes no appreciable loss of ascorbic acid. The most serious loss of vitamin C occurs when vegetables, including potatoes, are kept hot in insulated containers or in hot-plates. Some recent work has shown that less destruction of vitamin C takes place when the vegetables are kept hot in the water in which they are cooked Such treatment would scarcely improve their appearance or palatability, and potato soup might readily result in place of boiled potatoes! But the fact that there is less loss of ascorbic acid when vegetables are kept covered in liquid should be noted, for this is of practical value in the case of broth and stews Broth may be a very useful source of vitamin C if vegetables of the right kind are included. Surprising amounts of ascorbic acid were recorded when the water from cooked spring cabbage had been added to the soup. Parsley, turnips, swedes, cabbage, and green leaves of all kinds should be freely used in soups and stews, in addition to carrots.

Carrot is the vegetable most often put into stews, and unfortunately it is a very poor source of vitamin C, though it is a good source of vitamin A It is of interest that the carotene in cooked carrots is better absorbed than that from raw carrots, and that if carrots are grated they lose much of the small amount of ascorbic acid they contain

In preparing green vegetables for salads, they should be shredded with a sharp knife, preferably in ¼-½ inch shreds, and parsley should be coarsely chopped. If vegetables are grated or finely chopped there is a loss of vitamin C owing to the liberation of an oxidising enzyme from within the cells.

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nicotonic acid besides essential minerals, and it is not only vitamin C which may be lacking in the diet.

Lord Woolton has promised that all the food which is necessary for adequate school meals shall be forthcoming, and some Education Authorities are employing dietitians to organise the feeding in different areas. The school feeding centres are up against a very difficult problem. But I am sure that we shall only have satisfactory school feeding if enough money is spent on the dinners, if central kitchens are done away with, and if the serving of school meals is carried out, not by charwomen and school janitors, but by trained women who really care that the children should eat the food which is provided. The school dinner should be a truly protective meal with plenty of animal protein, vitamins and minerals. According to a circular issued by the Scottish Education Department, each dinner should average from 20 to 25 gms. of animal protein and 30 gms. of fat. This would represent from half to two-thirds of the child's daily animal protein requirement. The average value of the dinner is to be approximately 1000 calories with a reduction of 25 per cent. if the majority of the children are under eleven years of age, and a reduction of 33 per cent. if the children are under eight years. To provide a single meal of 700 to 1000 calories in war time entails the consumption of considerable amounts of bulky starchy foods, and it is often found difficult to persuade children to eat the full meal. It is probable that many children taking the school dinner are undersized and that their appetites are smaller than is the case with well-developed children. Calories can be obtained cheaply at home, but protein, vitamins and calcium depend chiefly upon the school dinner.

The full use of the allowances for fresh and dried milk and cheese at dinner would provide about 12 gms of animal protein, and the remaining 13 gms. could be supplied by 1½ oz. of cooked lean meat, or 2 oz. of fish. Pulses cannot entirely replace animal protein, as they are lacking in the amino-acid cystine Nevertheless, a small helping of meat will provide the necessary cystine, and pulse soups are useful when the meat ration is small.

The child's requirement for calcium will only be met if the milk at home and at school totals 1½ pints daily (30 oz.). It is therefore most desirable that the lunch milk and the school dinner should be taken, and that the war-time milk and cheese rations should also be provided at home

In the case of young children the supply of vitamins A and D

can be safeguarded by free cod-liver oil, dried eggs, and the milk ration, but for older children fatty fish should be included at home or at school, several times weekly, and vitamin A should be further increased by generous amounts of carrots, green vegetables, and liver when obtainable.

Vitamin C remains the most difficult problem. A school child should have about 60 mgs. of vitamin C daily, and about 40 mgs. of this should be given at the school dinner. This is quite impossible unless raw vegetable is served, or unless vegetables and potatoes are correctly cooked and eaten without being kept hot. Vegetable broth can also contribute useful, though very variable, amounts of vitamin C.

The following foods might provide some 40 mgs. of ascorbic acid :—

		Ascorbic Acid Mgs.
Cooked potato (not mashed)	5 oz.	5 (old) 25 (new)
Lightly cooked cabbage	3½ oz.	16
Water-cress	¼ oz.	5
Vegetable broth which includes cabbage water	½ pt.	10-15

Tomato and other raw salads and citrous fruits can, with advantage, replace vegetable broth when they are available, and the mother should complete the daily vitamin C requirement by serving more potato or salad at the evening meal.

It is not always realised that the vitamin C content of potatoes diminishes steadily the older they become. New potatoes may contain about 5 mgs. per oz. in the month of August, but old potatoes only 1 mg. in June.

There is an erroneous idea that lettuce is superior to cabbage as a source of vitamin C. Actually, the inner white leaves of lettuce may only contain about 5 mgs. of ascorbic acid per cent, the outer leaves about 9 mgs., while raw spring cabbage may contain from 80 to 110 mgs.

I am always hoping that we may discover some hidden and unsuspected virtue in the lettuce and in the apple, for at present one can find little justification for the adage of an apple a day keeping the doctor away. An apple of average size only contains about 4 to 6 mgs. of vitamin C. One-sixth of an ounce of raw cabbage might provide the same amount.

The benefits derived from a "protective" meal at school were well demonstrated some years ago in Oslo, and the excellent results of the Oslo breakfast were confirmed in feeding experiments in London. One group of children was used as a control,

and these children were given the usual hot school dinner, including milk. The children having the Oslo dinner were given 3 oz. wholemeal bread, a salad—using raw cabbage in winter—1½ oz. cheese, ¾ oz. butter, ¾ pint of milk, and a raw apple or orange. In the "Oslo group" the increase in height in the case of the boys was 25 per cent. greater than in the controls. In the girls the increase was 40 per cent. greater than in the controls. The improvement in weight in the "Oslo group" was 18 per cent. greater in the boys, and 26 per cent. greater in the case of the girls. The average concentration of hæmoglobin in the blood was 93 per cent. in the "Oslo group" against 81 per cent. in the other children. Unfortunately, the Oslo meal was not a universal favourite, and it was more costly than the usual school dinner chiefly because of the fresh fruit. In Scotland during most of the year a hot meal would seem to be desirable though less health-promoting. Nevertheless the principles of the Oslo protective meal should still hold good.

Nursery schools can do much to inculcate good feeding habits. This training is very necessary, for, at home, some children have rarely sat down at a table to eat their meals. Many children are not particularly interested in their food, and they prefer to run outside and play. In infancy they may have had a bottle thrust at them when they cried, or their appetites may have been spoiled by frequent jammy "pieces," a bar of chocolate, or a packet of potato chips

In my experience, the children who like the foods they ought to have are those who have been fed on a good mixed diet from an early age. Young children will be quite content to eat exactly the same meals day after day, and if this system is carried out they are suspicious of any new food which differs in flavour, colour or texture. The baby will immediately spit out a food to which he is not accustomed. The other day in a nursery school a small girl of two years carefully extracted the sultanas from her pudding, collected them in a little heap on the floor and, pointing to them, remarked, "Durrt"!

PREGNANCY.—While it is the child who is most susceptible to protein, mineral and vitamin deficiencies, we cannot expect to build a healthy race unless we have healthy mothers.

It is well known that a baby may be born with rickets or he may be predisposed to rickets, anæmia, and other ills if the mother's diet has been deficient in necessary food-factors during pregnancy and lactation An increased requirement for protein,

calcium, vitamin D and iron at such times is obvious, but in many cases no steps are taken to see that they are provided. Œdema, dental caries, and anæmia are some of the symptoms which may arise from such dietary deficiencies during pregnancy. Feeding experiments have been carried out on groups of pregnant women in Toronto and in this country, and there is considerable evidence to prove that a well-balanced diet during pregnancy has a favourable influence on the incidence of toxæmias and the number of live births. Moreover, in Toronto it was found that breast-feeding was carried out by 86 per cent. of the women who had been given supplementary rations during pregnancy, but in the control group only 59 per cent. were able to feed their babies. In most ante-natal clinics the doctor and the sister have not the time to give detailed instructions about diet. Here is a useful field for the dietitian. In Toronto it was found that in a third group of women whose incomes were satisfactory, it was well worth while giving dietary instruction even though no free supplementary rations were provided. I have always found that women are particularly co-operative during pregnancy, and much could be done by individual talks and by simple class instruction at this time.

It is true that if a woman has been in the habit of eating a good normal diet, little adjustment is required during pregnancy. In the later months an increase of some 10 to 20 per cent. in calories may be needed, unless activities are cut down. At the most, 480 calories might be necessary. One pint of milk will give 400 calories, and an extra egg or ¾ oz. of cheese will provide the other 80. By these additions the increased needs for calcium, phosphorus and protein will all be met.

The following foods would provide 90 gms of protein, including about 50 gms. of animal or first-class protein :—

		Protein
Milk—fresh, dried or evaporated . .	1½ pts.	30 gms
One egg (fresh or dried) or cheese . .	¾ oz.	6 „
Cooked meat (lean) or cheese or a herring	2 „	15 „
First-class protein . . .		51 gms.
Raw oatmeal for porridge .	1½ oz.	7 gms
Lentils .	1 „	6 „
Bread and scone .	6 „	18 „
Potato . .	6½ „	4 „
Fresh vegetables, cooked and raw (approx.)	8 „	4 „
Vegetable protein . .		39 gms.
Total protein		90 gms.

The question of protein is very important, and some 90 gms. should be included. In war-time this is by no means easy, and it is only possible if full use is made of the dried egg, cheese and meat rations, and if fish is included as often as possible.* Fish will also provide the extra iodine which is needed during pregnancy.

Cod-liver oil or vitamin capsules will supply additional vitamins A and D which are required during pregnancy, and the

TABLE I

Available Iron in servings of Common Foods

Food	Serving oz.	mgms.
Fried liver	3	18.45
Cockles	2	8.57
Fried sheep's kidney	one	3.3
Potato	8	3.18
Lentils - raw	2	2.86
Black treacle	1	2.6
Dried figs - stewed	4	2.57
Spinach	4	2.5
Leeks	4	2.28
Tinned peaches	4	2.2
Dried apricots - stewed	4	1.88
Raw oatmeal	1½	1.68
Germ bread	2	1.58
Egg	one	1.44
Broccoli tops	4	1.28
Dried peas, boiled	4	1.26
Wholemeal bread	2	1.22
Almonds	1	1.2
Fried herring	3	1.0
Prunes - stewed	4	0.92
Chocolate	1	0.8
Roast beef	3	0.74
Steamed haddock	3	0.6
Peanuts	1	0.58
White bread	2	0.48
Boiled carrot and turnip	4	0.43
Boiled cabbage	4	0.42
Chicken	2	0.33
Banana	2½	0.3
Apple or Orange	3½	0.24
Milk 1 glass, or cheese	1	0.16
Polished rice	1	0.11

priority allowance for oranges or concentrated orange juice will look after the vitamin C Naturally, the woman must be advised

* Recently the pregnant woman has been granted a child's meat ration in addition to her own, and the ordinary adult milk ration as well as the one pint of milk supplied on a priority basis

to take normal amounts of fats, dark grains such as oatmeal and brown bread, fresh vegetables and potatoes.

TABLE II

Calcium in servings of Common Foods compared to One Pint of Milk

Food	Serving	mgms.
Milk, whole or skim	one pint	682
Sprats, fried	2 oz.	402
Cheese, Cheddar	1 oz.	230
Broccoli tops, boiled	4 oz.	182
Beans, dried haricot, boiled	4 "	73
Cabbage, winter, boiled	4 "	66
Turnips, boiled	4 "	63
Haddock, steamed	3 "	46
Carrots, old boiled	4 "	42
Orange, raw - edible portion	3½ "	41
Parsnips, cooked	4 "	40
Cabbage, spring, boiled	4 "	34
Beetroot, boiled	4 "	34
Watercress	½ "	32
Brussel Sprouts	4 "	31
Herring, fried - whole	3 "	29
Egg	one	28
Cauliflower, boiled	4 "	26
Lentils, raw	2 "	22
Butter beans, dried boiled	4 "	21
Walnuts or peanuts	1 "	17
Vegetable marrow, cooked	4 "	16
Prunes, stewed	4 "	16
National Bread	2 "	15
Peas, fresh, cooked	4 "	14
Lettuce, raw	1½ "	11
Potatoes, old, boiled	8 "	10
Roast beef	3 "	6
Banana, raw - edible portion	2½ "	5
Apple, raw - edible portion	3½ "	3

Bread (other than National), cereals, and spinach - not included, as calcium they contain is unavailable.
Calcium in cooked vegetables depends upon hardness of water

It is seldom realised that milk and cheese are the only outstanding sources of calcium, and that it is essential to include 1½ pints of milk daily in order to ensure the 1·5 gms of calcium

which are necessary in pregnancy. Tables showing the calcium, phosphorus and iron content of foods are misleading, as not all of these minerals is assimilable. For example, in cereals much of the phosphorus is present in the form of phytin, and phytic acid forms insoluble calcium salts in the intestine which are excreted. The oxalic acid in spinach renders the calcium in this vegetable unavailable, and also affects the iron value. According to McCance, only 57 per cent. of the iron in spinach is available. Iron is seldom present in ideal amounts in the pregnant woman's diet. From 15 to 22 mgs. should be aimed at. Oatmeal, pulses and brown bread are useful and inexpensive sources. Additional iron can be provided quite cheaply by medicinal means.

Tables I and II show the iron and calcium content in servings of some common foods. The figures are arranged in descending order of merit.

You might think from this formidable array of figures that elaborate calculations are necessary in order to ensure a satisfactory diet. I fully realise that if a few guiding principles are followed, any sensible housewife can feed her family on a balanced diet, provided that the necessary foods are procurable and if she has the money to buy them. In war-time, ideals cannot always be attained, and the amount and kinds of foods which we eat are largely determined for us. I have drawn up a list of the foods which we should try to include in an *optimum* diet.

Adequate Normal Diet (Peace-time)

Daily.	
Milk (fresh, dried or evaporated)	Adults, ¾-1 pint Child, pregnancy, lactation, adolescence, 1½-2 pints. (Cheese ¾ oz. = milk ¼ pint in calcium value.)
Meat or fish or cheese	2-3 oz. (young children 1 oz.).
Egg (fresh or dried), *fatty fish*, or *liver*	Four times weekly. (Cheese, pulses, nuts, or bacon or white fish on other days.)
Vegetables . . .	Two servings : *one green or yellow*
Potato .	½-1 lb daily.
Fresh fruit or	One or two servings (one citrous or tomato).
Raw green vegetable	Good serving
Cereals and bread .	At least half the intake as dark grains.
Fats, butter, or vitaminised margarine	1-1¼ oz. (In war-time use full rations)
Cod-liver oil or concentrates	For children and mothers
Water . . .	Four glasses.

(Make up calories with sugar, jams, cake, dried fruits, and cooking fats)

Dietary Standards

There are occasions when doctors or dietitians have to plan or criticise diets on a more scientific basis both for persons in health and in cases of disease. More definite data is then needed in order to assess the probable requirement. I thought, therefore, that you might care to have a copy of the figures recently drawn up by the American National Research Council on Nutrition. You may not agree with all the standards which have been given, but they are at least a useful basis for discussion.

Dietary standards have, of course, not been fixed for all time, and they are likely to be modified as the science of nutrition advances. The American authorities are careful to point out that these allowances are for persons in health, and that requirements may vary very greatly in disease. When there is failure in absorption, or increased requirement due to fever and infections, or other causes, it may be impossible to meet the needs of the patient by means of an ordinary mixed diet, even if he were in a fit state to eat it. Vitamin concentrates must then be used. On the other hand, it is important to realise that a poor diet supplemented by all the vitamin concentrates which are on the market may still be lacking in some necessary nutrient.

You may wonder why I have made no mention of panto-thenic acid, pyridoxin, biotin, vitamins K and P and other factors Fortunately the foods which supply enough of what we may call the "major vitamins" will also include the less well-known substances.

It is not my purpose this afternoon to discuss the chemistry or functions of the vitamins, minerals, proteins or other constituents in the diet, even if I were qualified to do so; but, before concluding, there are one or two practical points which I should like to mention.

Calories.—Many of us can well afford to forgo the 400 to 500 calories which are lost by the rationing of meat, fats, sugar, jam and bacon. The average man or woman can still get all the calories he or she requires by a compensatory increase in starchy foods. On the other hand, it may be difficult to make up for the decrease in sugar, protein and fats when really high calories are needed for growth or for hard work. This drop in calories may be detrimental, especially in the case of active young men and women There is a limit to the amount of bulky

TABLE III

Extract from Figures recommended as Daily Allowances for Specific Nutrients by Committee on Foods and Nutrition, National Research Council, U.S.A.

	Calories	Protein. Grams	Protein. Alternative * Not less than 1 gm per K B W. Grams	Protein. Alternative * Grams	Calcium Grams	Iron Mg	Vitamin A † I U	Thiamin (B_1) ‡ Mg	Riboflavin Mg	Nicotinic Acid Mg.	Ascorbic Acid ‡ Mg	Vitamin D I.U.
Man (70 kgs)			10 per cent of total cals	12 per cent of total cals								
Moderately active	3000	70	75	90	0 8	12	5000	1 8	2 7	18	75	‖
Very active	4500	70	112	135	0 8	12	5000	2 3	3 3	23	75	. .
Sedentary	2500	70		75	0 8	12	5000	1 5	2 2	15	75	. .
Woman (56 kgs)												
Moderately active	2500	60	63	75	0 8	12	5000	1 5	2 2	15	70	‖
Very active	3000	60	75	90	0 8	12	5000	1 8	2·7	18	70	
Sedentary	2100	60		63	0 8	12	5000	1 2	1 8	12	70	...
Pregnancy (latter half)	2500	85			1 5	15	6000	1 8	2 5	18	100	400-800
Lactation	3000	100			2 0	15	8000	2·3	3 0	23	150	400-800
Children up to 12 years			15 per cent of total cals Grams									
Under 1 year	100 per kg	3 4 per kg			1 0	6	1500	0·4	0 6	4	30	400 800
1 to 3 years §	1200	40	40 to 45		1 0	7	2000	0 6	0 9	6	35	‖
4 " 6 "	1600	50	50 " 60		1 0	8	2500	0 8	1 2	8	50	.
7 " 9 "	2000	60	60 " 75		1 0	10	3500	1·0	1 5	10	60	. .
10 " 12 "	2500	70	70 " 94		1 2	12	4500	1 2	1 8	12	75	. .
Children over 12 years			From 12 to 15 per cent of total calories									
Girls 13 to 15 years	2800	80			1 3	15	5000	1 4	2 0	14	80	‖
" 16 " 20 "	2400	75			1 0	15	5000	1 2	1 8	12	80	.
Boys 13 " 15 "	3200	85			1 4	15	5000	1 6	2 4	16	90	
" 16 " 20 "	3800	100			1 4	15	6000	2 0	3 0	20	100	

* An alternative column for protein allowances has been added
† Requirements may be less if provided as vitamin A, greater if provided chiefly as the pro-vitamin carotene.
‡ One mg thiamin equals 333 I U, 1 mg ascorbic acid equals 20 I U.
§ Allowances are based on needs for the middle year in each group (as 2, 5, 8, etc) and for moderate activity
‖ Vitamin D is undoubtedly necessary for older children and adults. When not available from sunshine it should be provided by the minimum amounts recommended for infants.

carbohydrate which can be taken, and besides, porridge needs milk, and dry bread is not an attractive proposition.

Owing to the cut in protein and fat, meals have become much more bulky, and workers cannot take all the calories they need unless they eat more frequently. In the interests of health and efficiency it has been found worth while to provide more frequent meals for factory workers, and many of my out-patients have remarked how much they appreciate the extra milk which they receive at their work.

The increased food allowances which are issued to canteens for heavy workers are essential, for in the last war it was recorded that some young girls working in munitions ate as much as 3800 calories per day. Unfortunately, in many cases it is difficult to persuade employees to eat the canteen meal instead of lunching on "a carried piece."

PROTEIN.—The protein figures on the American chart call for some comment. In the case of the average man, the standard figure of 70 gms. is satisfactory when only moderate calories are needed, but it can hardly be considered adequate when high calories are required. I have therefore entered an extra column on Table III suggesting a rather different scale for protein, and this will, I think, be found to be more practical in compiling satisfying and varied diets. The American authorities do not stipulate that the protein should not be more than 70 gms., and in a low-cost diet which they give the protein figure is 93 gms

In this country, *unless protein is restricted for therapeutic* purposes, or by reason of war or poverty, it is usual to reach some 1·5 gms. per K.B.W, that is, about 90–100 gms per day in the case of an active man. A man engaged in hard physical work might take 70 gms. protein from 1 lb. bread and scones, 1 lb. potato, 2 oz. oatmeal, some vegetables, and a plate of lentil soup This allows nothing for milk, cheese, eggs, fish or meat. On the other hand, a man engaged in a sedentary occupation might eat only half this amount of protein from vegetable sources.

It seems reasonable, therefore, that protein intake should be in some way related to the calories and not fixed at an arbitrary figure according to body weight It is believed that, *theoretically*, protein requirement does not increase because of muscular work. This may be a physiological fact, but it is not true from the psychological angle.

Now, 70 gms. of protein in a diet of 3500 calories represents

only 8 per cent. of the total calories. In a diet of 4500 calories it represents only 6 per cent. Even in countries where the diet consists entirely of grains and vegetables, some 11 per cent. of the total calories is usually derived from protein. It does not seem unduly extravagant, then, to take 10 to 12 per cent. of the total calories as a protein standard for the adult, and you will see from Table III that 12 per cent. would provide up to 90 gms. of protein in a diet of 3000 calories. In the case of young children, 15 per cent. of the total calories will be found to be a better figure if 1½ pints of milk are to be included in the diet, for the milk alone gives 30 gms. protein. The figure given for adolescent youths would seem to be low. The Technical Committee of the League of Nations suggested 2 gms. of protein per K.B.W. A well-grown boy of sixteen to seventeen years would therefore need about 120 gms. of protein daily, which is in accordance with the amount eaten in most boarding-schools.

There is no exact scientific data upon which to fix the amount of animal protein which should be provided. This depends to a great extent upon a judicious combination of vegetable protein. From 37 to 50 gms. of animal protein is a very satisfactory range. In war-time the lower figure must certainly be adopted, at any rate for the adult, and most authorities consider that this should be adequate. Many diets, especially in the case of women, contain much less animal protein—sometimes under 20 gms. The lower intake in the case of women is partly due to the fact that the major share goes to the hungry male, and it is not unusual to find that the women and younger children have only the gravy from the meat. Apart from pregnancy and childhood, a low intake of protein is most serious in the case of adolescents, but protein is important at all ages, since it is required not only for growth but also for maintaining a high resistance to infection and for the prevention of anæmia. A good intake of animal protein ensures also an adequate supply of certain other nutrients. If milk is taken in satisfactory amounts, and if the rest of the animal protein is generous, the available calcium, phosphorus, riboflavin and nicotinic acid will all be assured. If first-class protein is low, all these factors will be found to be poor.

The B_2 complex is undoubtedly helped also by succulent green vegetables and by whole-grains which contain the germ The National loaf has not only improved the B_2 intake, but it has removed any serious danger of lack of thiamin (B_1), besides increasing the amounts of iron and calcium in the diet.

We have seen that great care needs to be taken in respect of *vitamin C*, but that it is not impossible, even in war-time, to obtain an adequate intake if large quantities of potato and bulky vegetables can be eaten. For the dyspeptic or for the seriously ill patient, pure ascorbic acid is essential in the absence of fresh orange juice.

Vitamins A and D.—The fat-soluble vitamins are both very low at the present time, chiefly owing to the restriction in fat. Even though vitamins A and D have been added to margarine, it only contains 500 I.U. of vitamin A per ounce, and 60 I.U. of vitamin D. Scottish summer butter contains on an average about 800 I.U. of vitamin A and only 25 of vitamin D (sometimes less). The combined margarine and butter rations will only contribute about one-tenth of the daily requirement for vitamin A, and one-sixth of the daily requirement for vitamin D (estimated at 250 I.U. daily). This leaves a considerable balance to be procured from other foods. Moreover, when vitamin A is derived from the carotene of vegetables and not from fats, the intake is much less certain and more vitamin A is required; *e.g.* it is probable that only one-third of the vitamin A listed in carrot is actually used.

In peace-time, fresh fruit, fats, fresh eggs, liver and fish are all available in generous amounts. In war-time we must make full use of dried egg, cheese, canned fatty fish, green vegetable, tomatoes and carrots. Even in peace-time many diets contain only about one-third to one-half of the vitamin A requirement.

It may be that the adult requirement for vitamin D is less than is generally supposed, but it is difficult to see how we are to get enough vitamin D in this sunless climate when eggs and fatty fish are scarce, and fats are restricted The intake is often well below 100 I.U., while 250 to 400 have been quoted as desirable. The low intake of vitamin D might well prove disastrous to older children who are not usually given cod-liver oil, and it can hardly be considered as satisfactory in cases of fractures or in many pathological conditions.

Conclusion

In conclusion, I must make it clear that I have no official information about the adequacy of the nation's diet at the present time My statements are chiefly based on the results of

only 8 per cent. of the total calories. In a diet of 4500 calories it represents only 6 per cent. Even in countries where the diet consists entirely of grains and vegetables, some 11 per cent. of the total calories is usually derived from protein. It does not seem unduly extravagant, then, to take 10 to 12 per cent. of the total calories as a protein standard for the adult, and you will see from Table III that 12 per cent. would provide up to 90 gms. of protein in a diet of 3000 calories. In the case of young children, 15 per cent. of the total calories will be found to be a better figure if 1½ pints of milk are to be included in the diet, for the milk alone gives 30 gms. protein. The figure given for adolescent youths would seem to be low. The Technical Committee of the League of Nations suggested 2 gms. of protein per K.B.W. A well-grown boy of sixteen to seventeen years would therefore need about 120 gms. of protein daily, which is in accordance with the amount eaten in most boarding-schools.

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HÆMOLYTIC ANÆMIAS *

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THE object of this lecture is to survey some of the recent views on the hæmolytic anæmias. The renewed interest displayed in these disorders during the past few years, however, has resulted in a literature so voluminous that it is impossible in the time available to attempt even a superficial survey of the group as a whole. Consequently it is proposed to limit the subject-matter to a brief consideration of some fundamental principles involved in all types of hæmolytic anæmia, and to a short discussion of certain syndromes which have attracted recent attention. Only a passing reference will be made to views and facts that are firmly established or widely known.

Obviously it is desirable to commence by defining the term hæmolytic anæmia. This is easy if one is content with a theoretical concept. A hæmolytic anæmia is clearly one in which the anæmic state results mainly from the process of blood destruction proceeding more rapidly than blood regeneration can keep pace with.

It is much more difficult, however, to supply a formula of general value in clinical diagnosis For it must be borne in mind that the opposing forces of blood formation and blood destruction react upon each other. Excessive destruction results in abnormal production, while the generation of abnormal red cells may result in their accelerated destruction Not so long ago pernicious anæmia was regarded as a hæmolytic process, but now it is considered that the anæmia in this condition is due to defective erythrocyte maturation, and that any excessive red cell destruction that may operate plays but a secondary rôle.

While in some types of hæmolytic anæmia a diagnosis may readily be arrived at, in others it may require careful assessment of the findings of a thorough clinical and laboratory investigation. Such an investigation should include, in addition to a careful physical examination, the taking of a detailed personal and family history, a study of the peripheral blood and the sternal marrow, and a search for evidence of increased or abnormal blood destruction

* Read 9th September 1943

my own observations, and I must repeat that the food deficiencies which I have mentioned are not merely due to a war-time food supply.

The effects of dietary deficiencies are insidious. It has been rightly said that the constant drop of water will wear away a stone. The constant imperfections of nutrition, be they ever so slight, will eventually take their toll. In our post-war policy we must aim at an optimum figure for every nutrient in the diet for every country in the world and for every class.

After nearly four years of war we have much to be thankful for, and I feel sure that, should the occasion arise, we in Britain will gladly sacrifice some of our own abundant food supply to feed the starving peoples of the liberated countries of Europe and of Asia.

1901; Josephs, 1938), that normal serum is capable of inhibiting hæmolysis. Accordingly they suggest that normal hæmolysis may be governed by a balance between the lytic agent and the serum inhibitor, and that reduction in the latter may be the cause of pathological hæmolysis.

Whatever be the mechanism responsible for red cell destruction it is generally agreed that the resulting damaged cell or its débris is disposed of by the phagocytic cells of the reticulo-endothelial system, a large proportion of which is located in the spleen. In short, while it is unknown whether the spleen is the slaughter-house of the red cell, there is a general consensus of opinion that it does serve as its graveyard.

Following phagocytosis of the débris, the iron is split off from the hæmoglobin and is transported by the plasma to the bone-marrow where it is utilised, and to the liver and other tissues where excess is stored

The iron-free compound is converted by a series of unknown steps into bilirubin which passes into the plasma, probably in combination with serum protein (Barron, 1931). This combined bilirubin or hæmo-bilirubin, as it may conveniently be called, is incapable of passing the kidney filter, and reacts with Ehrlich's reagent only after treatment with alcohol. A small quantity remains in the circulation; most of it, however, is filtered off by the liver, where it is converted into an alkaline salt and excreted in the bile as hepato-bilirubin.

In the intestine this hepato-bilirubin is reduced by bacterial action to urobilinogen, or stercobilinogen as some call it. It seems probable that a proportion of the urobilinogen is absorbed from the intestine into the portal circulation, carried to the liver and mostly re-excreted into the bile. A very small proportion enters the systemic circulation and may escape into the urine. In health about 0·5-2 mgms. urobilinogen may be excreted in the urine daily, while 40-280 mgms are excreted in the fæces (Watson, 1939). In the fæces and urine urobilinogen is oxidised into urobilin

Under conditions of excessive red cell destruction the production of hæmo-bilirubin will obviously be increased. If this increase be within the capacity of the liver to handle it, the only demonstrable result may be a raised output of fæcal urobilinogen which may or may not be accompanied by increased excretion of urobilinogen in the urine. If, however, the production of bilirubin exceeds this limit, an augmented quantity of hæmo-

For a discussion of the various manifestations of excessive blood destruction to be intelligible, the underlying mechanisms concerned with the disposal of red cells and hæmoglobin in health and disease require consideration.

The normal mechanism of red cell destruction is not known with certainty.

It seems unlikely that phagocytosis by the cells of the reticulo-endothelial system normally plays a major rôle (Knisely, 1936). Nor is there convincing evidence that a circulating hæmolysin is responsible. The explanation most generally accepted is that the cells undergo fragmentation as a result of the physical stresses to which they are subjected in the circulation (Rous, 1923).

Reference, however, should be made to two further possibilities that have recently been suggested. Firstly, there is the possible rôle of lyso-lecithin, a substance which exerts a direct lytic action on red cells. Its biological significance was demonstrated by Kellaway (1939), who showed that the hæmolytic effect of Australian cobra venom depends upon the action of lecithinase in removing an unsaturated fatty acid molecule from serum lecithin and so converting it to lyso-lecithin. Furthermore, it was found by Bergenhem and Fåhraeus (1936) that minute quantities of lyso-lecithin are present in normal human plasma; and that if plasma be incubated *in vitro* for a few hours under static conditions its lyso-lecithin content increases 2-8 times, apparently due to the action of serum-lecithinase.

This observation led to the suggestion (Fåhraeus, 1939) that stagnation of blood in the spleen might result in its lyso-lecithin content being raised and so favour hæmolysis in this site under normal conditions, and also explain the increased hæmolysis in certain hæmolytic disorders associated with enlargement of the spleen and presumably increased stagnation of blood. Singer (1941), however, has found no evidence of increased lyso-lecithin production in cases of familial acholuric jaundice. Furthermore, Foy and Kondi (1943) found no evidence of hæmolytic action *in vivo* following the intravenous injection into baboons of relatively huge amounts of lyso-lecithin. The possible significance of lyso-lecithin in red cell destruction in health or disease is therefore at present hypothetical.

A few months ago Macgraith *et al.* (1943a) demonstrated the presence of a hæmolytic agent, probably an enzyme, in washed tissues from a variety of organs both human and animal. These authors also confirmed the findings of earlier workers (Besredka,

Fairley and Bromfield, 1937). Fairley (1941) has shown that the hæmatin combines with the serum albumin to form met-hæmalbumin. Met-hæmalbumin has a large molecule and never escapes in the urine. It is, however, probably eliminated by the liver as coproporphyrin III (Rimington, 1939). Met-hæmalbumin may be demonstrated in the plasma by suitable spectroscopic tests, and its presence is a conclusive indication of intravascular hæmolysis.

When the degree of intravascular hæmolysis is sufficient to produce marked hæmoglobinæmia, hæmoglobin may pass the kidney barrier and appear in the urine. It seems that there is a renal threshold for hæmoglobin of about 150 mgms. per 100 cc. plasma (Gilligan *et al.*, 1941). Once hæmoglobinuria is established, however, it may continue in the presence of a plasma hæmoglobin concentration as low as 30-50 mgms. per 100 cc.

Hæmoglobinuria thus may be regarded as an indicator of intravascular hæmolysis.

Among the clinical and pathological manifestations that may accompany or result from prolonged excessive blood destruction are: enlargement of the spleen consequent upon the hyperplasia of the reticulo-endothelial components of that organ; the formation of gall-stones of the pigment variety due to hyperbilirubinæmia; and siderosis, which is a common finding post-mortem.

Backache, malaise rigor and vomiting are often noted in acute intravascular hæmolysis.

Increased red cell destruction results in accelerated blood regeneration. There is experimental evidence for believing that when, as in hæmolytic anæmias, the red cell destruction does not result in immediate loss to the body of certain hæmoglobin derivatives, regeneration is more active than when the hæmoglobin escapes as in hæmorrhage. It is probable that bilirubin may act as a stimulus to the marrow (Bomford, 1940).

Accordingly, then, in hæmolytic disorders evidence of sustained red cell regeneration is a finding of diagnostic importance.

In the peripheral blood this regeneration is reflected by an increased immaturity of the red cell population, which may be recognised by the following features.

1. *A sustained high reticulocyte count*—A reticulocyte count exceeding 1-2 per cent. is rarely found in health. Higher counts indicate abnormal marrow activity but not necessarily associated with increased hæmolysis.

It is widely recognised that a sustained low-grade reticulo-

bilirubin is retained in the circulation, giving rise to clinical and chemical evidence of hæmolytic or retention jaundice, and because of the inability of the liver to re-excrete the larger amounts of urobilinogen absorbed from the gut, excessive amounts are excreted in the urine.

It will be apparent that the functional capacity of the liver plays an important part in determining how these manifestations develop. Hepatic inefficiency may in fact give rise to jaundice and increased urobilinogen in the urine in the absence of increased hæmolysis. Such a condition, however, will not result in an increased urobilinogen excretion in the fæces. The quantitative determination of the fæcal urobilinogen output is therefore a valuable test, since if the reading is abnormally high it may be concluded that red cell destruction is excessive, while a normal or reduced reading in the presence of a raised excretion of urobilinogen in the urine indicates hepatic dysfunction. This of course is the basis of the urobilinogen test for liver function.

It must be remembered, however, that such manifestations of hepatic dysfunction may result from the anoxæmic effects produced by a severe anæmia. The icterus of pernicious anæmia is probably in no small degree due to this. A raised production of bilirubin and urobilinogen may also result from purely local blood destruction such as occurs in a hæmatoma.

It is unfortunate that quantitative fæcal urobilinogen determinations are not more widely available, since their employment in the study of hæmolytic disorders constitutes one of the most important of recent technical advances in this field.

The foregoing considerations are chiefly relevant to quantitative variations of red cell destruction in which the final breakdown is dependent upon an *intracellular mechanism*.

Under certain pathological conditions, however, the site of hæmolysis may be predominantly or exclusively intravascular, resulting in the liberation of free hæmoglobin in the general circulation.

The reticulo-endothelial cells are capable of absorbing and dealing with small amounts of free hæmoglobin, and so, if the degree of intravascular hæmolysis be but slight, the only observable effects may be an increased bilirubinæmia and excretion of urobilinogen

When larger amounts of hæmoglobin are present in the plasma than can be removed by the reticulo-endothelial cells, the excess breaks down into hæmatin and globin (Fairley, 1940a;

(1933) produced experimental anæmia in two groups of rabbits by repeated bleedings. In one group the hæmoglobin obtained from the bleedings was injected back into the animals. In this group a macrocytic anæmia resulted, while the other group, where the hæmoglobin was permanently lost, developed a microcytic anæmia. The conditions obtaining in the first group are of course analogous to those in hæmolytic anæmia.

Since red cell regeneration is frequently shared by the other cellular elements of the marrow, leucocytosis with a relative increase in the proportion of young granulocytes and an increase in the platelet count are commonly found in hæmolytic anæmias. In some forms, however, a leucopenia is present.

The marrow, examined during life by sternal puncture, or at post-mortem, shows hypercellularity, and hyperplasia with a relative increase in the proportion of red cell precursors which are of the *normoblastic type, and which may display premature* hæmoglobination (Israels, 1941)

In some types of chronic hæmolytic anæmia the hyperplasia of the marrow may result in absorption or expansion of the adjacent bone.

The fæces show an increase in the content of coproporphyrin I (Dobriner *et al.*, 1937).

It will be apparent that of the various findings that may occur in a hæmolytic anæmia, only the following can be regarded as unequivocal evidence of excessive or abnormal blood destruction: (1) increased excretion of fæcal urobilinogen; (2) methæmalbuminæmia; (3) hæmoglobinuria.

Unfortunately facilities for demonstrating the first two are not widely available, while the last is seen only in certain types of intravascular hæmolysis

For the most part, then, we are dependent for diagnosis on the assessment of a number of findings which must be considered in relation with each other and with such further data as may be obtained from the individual patient.

Classification

Although many classifications of hæmolytic anæmias have been proposed, none can be regarded as satisfactory. This is inevitable in view of the present imperfect state of our knowledge concerning the ætiology and pathogenesis of the diverse morbid states which are believed to result from excessive blood destruction.

cytosis may occur in anæmia due to chronic hæmorrhage and in leuco-erythroblastic anæmia, but it is perhaps less widely known that a sustained reticulocyte count of around 5 per cent. may be encountered in certain types of anæmia due to marrow hypoplasia. A patient suffering from such an anæmia under Dr W. A. Alexander's care has been observed by the writer for nearly two years, and for weeks at a time she has shown a reticulocyte count varying from 4 to 7 per cent. The probable explanation is that regenerative activity is maintained by scattered foci of cellular marrow in an attempt to compensate for the remaining hypocellular marrow.

In hæmolytic anæmias a sustained reticulocyte count exceeding 10 per cent. is common in the more chronic types, while in the more acute forms the figure may be considerably higher, even as high as 90 per cent.

It is scarcely necessary to add that in ordinary Romanowsky stained blood films reticulocytosis is characterised by the appearance of polychromasia.

2. *Nucleated red cells* are often seen in the more acute types of hæmolytic anæmia, particularly in the hæmolytic anæmias of childhood

3. *Anisocytosis* is usually a prominent feature in active blood regeneration, but is not necessarily accompanied by poikilocytosis.

Anisocytosis is particularly marked in familial acholuric jaundice on account of the presence of numerous microspherocytes. These cells, however, are, broadly speaking, peculiar to this type of hæmolytic anæmia and are not characteristic of red cell regeneration.

4. *Macrocytosis* is evident in a number of forms of hæmolytic anæmia. In some cases the macrocytic appearance of the blood picture may be due to the large numbers of reticulocytes which always tend to have a larger diameter than the more mature cells. Such appearances have accordingly been termed "*pseudo-macrocytic*" by Dameshek and Schwartz (1940). In other cases, however, the degree of macrocytosis is not necessarily related to the degree of reticulocytosis (Fowler, 1941), and a true macrocytic picture is found.

The mechanism of the production of macrocytes by a normoblastic marrow is not properly understood. Davidson and Fullerton (1938) have suggested that it may be explained by the premature maturation of unduly stimulated normoblasts. In this connection it is of interest to note that Miller and Rhoads

difficult to avoid reference to certain aspects of this disorder, since its established position in the literature renders it a sort of point of departure for charting discoveries amongst the lesser-known hæmolytic conditions.

Jaundice due to excessive hæmolysis as distinct from that due to biliary obstruction was first described by Hayem in 1898, and the recognition of hæmolytic jaundice with a familial incidence is ascribed to Minkowski in 1900. The characteristic increased red cell fragility of familial hæmolytic jaundice was subsequently described by Chauffard (1907), whose name is often associated with the condition.

During this period Widal and his associates (1907) described a number of cases in which no familial tendency could be discovered. To distinguish such cases the term " acquired hæmolytic anæmia " came into general use. Accordingly, for many years it was customary to classify hæmolytic anæmias into two varieties : the congenital or familial form of Chauffard, and the acquired form of Widal. It is now, however, becoming widely recognised that the latter designation comprises a heterogeneous group of syndromes differing widely in their ætiological, hæmatological and clinical aspects.

The familial form, on the other hand, has become firmly established as a clinical entity, with features that may be summarised as follows.

The disorder which is inherited as a Mendelian dominant manifests itself by recurrent hæmolytic crises varying greatly in frequency and severity. These attacks usually commence during the first decade, although they may occur in early childhood or be delayed until later adult life. Not all the members of a tainted family are affected, but some of those who escape may show characteristic hæmatological abnormalities.

The intensity of the jaundice which develops during a crisis is variable and not necessarily proportional to the degree of accompanying anæmia. The spleen is usually enlarged, gall-stones are frequent, while bone changes and ulceration over the legs are occasionally present. Hæmoglobinuria or other evidence of intravascular hæmolysis is not seen. Bilirubinuria is of course not present in uncomplicated cases.

The anæmia may be severe during a crisis, but usually is only moderate in degree. The colour-index remains around unity, but anisocytosis is marked. A characteristic finding is the presence of large numbers of small deeply staining red cells, the micro-

The classification adopted in this lecture is based on factors that are thought to be of ætiological significance, but it must be emphasised that the schedule is to be regarded solely as a provisional expedient.

HÆMOLYTIC DISORDERS

Arranged according to Known or Supposed Ætiology

1. ABNORMALITY OF THE RED CELLS	
Familial acholuric jaundice	Microspherocytosis
Sickle cell anæmia	Sickling trait
Nocturnal hæmoglobinuria	*p*H factor
2. HÆMOLYSINS	
Transfusion incompatibility	Iso-antibodies; Rh factor, etc
Erythroblastosis fœtalis, etc.	Rh. factor
Paroxysmal hæmoglobinuria	"Cold lysins"
In severe burns	Protein cleavage products
Bacterial infections	Hæmolytic toxins: Cl. welchii, staphylococci, streptococci, etc
Snake bite	Cobra venom
3 PARASITIC INFECTION OF RED CELLS	
Malarial anæmia	Plasmodium sp.
Oroya fever	Bartonella bacilliformis
4 POISONS EXERTING LYTIC OR OTHER ACTION ON RED CELLS	
Lead; phenylhydrazine, arsenuretted hydrogen; phenothiazine, arsenical compounds; ricin, saponin; promin, etc.	
5 HYPERSENSITIVITY TO DRUGS OR OTHER AGENTS	
Sulphonamide anæmia	
Fabismus	Vicia faba (horse bean)
Baghdad spring anæmia	Pollens
6 CAUSE UNKNOWN BUT ASSOCIATED WITH KNOWN PREDISPOSING FACTORS	
Blackwater fever	Sub-tertian malaria
"Symptomatic" hæmolytic anæmias	Hodgkin's; reticuloses; carcinoma, etc.
March hæmoglobinuria	Postural defect
7 CAUSE COMPLETELY UNKNOWN	
Acute hæmolytic anæmia	"type Lederer" so called
Miscellaneous subacute and chronic hæmolytic anæmias	
Cooley's (Mediterranean) anæmia	

I *Hæmolytic Anæmias due to Abnormality of the Red Cells*

Familial Acholuric Jaundice (congenital hæmolytic icterus) is one of the few hæmolytic disorders of which the clinical and hæmatological features have been sufficiently studied to warrant its recognition as a definite clinical entity. The nature of these features, moreover, is so well known that a detailed discussion of them is superfluous in a review such as this. Nevertheless it is

erythropoiesis resulting in the production of abnormal spherocytic red cells. The persistence of increased fragility after splenectomy is thought to support this hypothesis, the subsequent cessation of increased hæmolysis being explained by the removal of the chief site of red cell destruction.

According to the second hypothesis the red cells are normal when they first enter the circulation, but are subsequently affected by some agency, such as a circulating hæmolysin produced in the spleen. Dameshek and Schwartz (1940) are the chief protagonists of this contention and advance in its support the following considerations. Spherocytosis and increased fragility have been observed to develop in normal red cells as "pre-lytic" phenomena on exposure to certain lytic agents such as lyso-lecithin and hæmolytic serum. Furthermore spherocytosis has been observed in acquired or idiopathic hæmolytic anæmias, and it is claimed (Dameshek and Schwartz, 1938*b*; Tiggert *et al.*, 1940) that the injection of homologous hæmolytic sera into animals in suitable doses results in hæmolytic anæmia with increased red cell fragility and spherocytosis

However, such observations merely show that spherocytosis can be acquired under certain conditions. No satisfactory evidence for the existence of circulating hæmolysins in familial acholuric jaundice has been presented, although accelerated autohæmolysis *in vitro* has been demonstrated (Dacie, 1941). It was observed by Singer (1940) that in familial acholuric jaundice the red cells displayed increased fragility to lyso-lecithin, but reference has already been made to the same author's subsequent failure to demonstrate increased lyso-lecithin production in this disease (Singer, 1941).

A few months ago Dacie and Mollison (1943) found that erythrocytes from a case of familial acholuric jaundice taken both before and after splenectomy when transfused into normal individuals disappeared with undue rapidity, whereas when normal cells were transfused into patients with familial acholuric jaundice their survival times were normal. This observation clearly affords strong support for the view that the essential abnormality lies in the red cells. Nevertheless the available evidence is too fragmentary and conflicting to warrant the rejection of the possibility of some abnormal hæmolytic mechanism being involved.

It is evident that the problem of pathogenesis in acholuric jaundice requires further investigation for its solution.

spherocytes. These cells usually constitute about 20 per cent. of the total red cells present. Because of their small diameter the mean cell diameter of the blood is significantly reduced, but on account of their globular shape the mean cell volume usually remains normal (von Boros, 1926). The presence of these cells is so constant a finding that Krumbhaar (1936) has suggested for the disease the designation " spherocytic jaundice."

Reticulocytes are present in significantly increased numbers, but their frequency shows variations during the course of the disease, being increased during the crises On occasion very high counts may be noted.

In the great majority of cases the red cells display increased fragility to hypotonic saline. This finding, together with that of microspherocytosis, is present throughout the life of an affected individual and is unaffected by the occurrence of hæmolytic crises.

The patients may enjoy good health during the periods of remission but severe crises are often fatal. Of 40 cases studied by Dawson (1931) 12 died

Splenectomy is now generally recognised to be the treatment of choice. It is immediately followed by cessation of increased hæmolytic activity with subsequent disappearance of jaundice and anæmia. The increased fragility of the red cells usually persists, however, although it may occasionally be reduced or increased (see Dacie, 1943). The microspherocytes also remain in the peripheral blood and have been demonstrated as long as sixteen years after splenectomy (Thompson, 1936), but it has been claimed that they become reduced in number (Whitcher, 1925; Hawkesley, 1935), and that in 50 per cent. of patients they may eventually disappear (Vaughan, 1937)

The mechanism of the increased hæmolysis in familial acholuric jaundice has naturally engendered much speculation. The demonstration by Haden (1934, 1941) that the fragility of red cells in hypotonic saline is a function of the degree of spherocytosis provides a reasonable explanation of the increased fragility noted in this disease. Whipple (1941) has suggested, furthermore, that the rotund shape of the spherocytes may retard their passage through the capillaries of the spleen, thus prolonging their exposure to such potentially destructive agencies as phagocytosis and lyso-lecithin.

Two main theories have been advanced concerning the causation of the spherocytosis. The older view supported by Chauffard and by Naegeli (1931) is that the inherent defect lies in

considerable light on the pathogenesis of the condition. It has been shown that the washed red cells of patients may undergo hæmolysis when exposed to serum either from patients or from normal individuals, and that the degree of hæmolysis is increased if the serum be slightly acidified. The hæmolytic principle is inactivated by heat and is not reactivated by guinea-pig complement.

It is evident that the hæmolytic mechanism in this disorder results from an abnormality of the red cells which renders them peculiarly susceptible to lysis by some agent normally present in the plasma, probably human complement; and that this susceptibility is aggravated by an increased hydrogen ion concentration such as occurs during sleep consequent upon reduced pulmonary ventilation (Kleitman, 1929).

It has been shown by Ham (1939) and others that clinically the degree of hæmolysis may be increased temporarily by ingestion of ammonium chloride and decreased by alkalisation induced by hyperventilation or by administration of alkaline salts.

The prognosis of these cases is grave, but a number are known to have survived for several years after the onset of symptoms.

Treatment is unsatisfactory. A liberal fluid intake is obviously desirable in the presence of hæmoglobinuria, and the administration of alkalis merits trial. Blood transfusions should be given when the anæmia is severe, for it has been shown by Dacie and Firth (1943) that although transfusion may be followed by an exacerbation of hæmolysis of the patient's cells, the survival of the transfused cells is unimpaired, the net result being beneficial.

Splenectomy is of very doubtful value. Since the site of hæmolysis is primarily intravascular there is no obvious rational basis for removal of the spleen. Moreover the reported results are far from encouraging. Of 16 cases in which splenectomy has been reported, only 2 derived any apparent permanent benefit (Donati, 1930; Dacie *et al.*, 1938), 7 died during the post-operative period, while in the remaining cases the anæmia appeared to be unaffected, although it has been claimed that the severity of the noctural hæmoglobinuria was ameliorated in 2 of them (Ham, 1937; Ham and Horack, 1941).

By the courtesy of Dr T. R. R. Todd an opportunity recently arose of studying an example of this condition.

Case History.—The patient, a male shop-assistant, aged 29, was admitted to hospital complaining of shortness of breath of three months' duration. Six years previously pernicious anæmia had

Sickle-cell Anæmia is practically confined to the negro race and is accordingly of little importance in this country. In the United States, however, it has attracted considerable attention. While the mechanism of hæmolysis is still unknown, it is generally agreed that the essential factor lies in a hereditary tendency of the red cells to become crescentic in outline under certain circumstances.

Nocturnal Hæmoglobinuria, a form of chronic hæmolytic anæmia characterised by attacks of hæmoglobinuria, usually occurring at night or during sleep, was reported by Marchiafava and Nazari (1911), and more fully described, after an analysis of 13 cases, by Micheli (1931). The condition is accordingly often named the syndrome of Marchiafava-Micheli. The disorder is uncommon, only about 40 cases having been reported to date, but it is probable that many cases escape recognition since the hæmoglobinuria may be slight in degree and transient in duration. Indeed, the convention of classifying this disorder as a paroxysmal hæmoglobinuria is to be deprecated, since the hæmoglobinuria is an incidental manifestation dependent upon the degree of red cell destruction.

The essential feature is a chronic hæmolytic anæmia often of considerable severity and displaying a fluctuating course. The blood picture is usually macrocytic, and microspherocytosis is not seen. The reticulocyte count is persistently high, fragility to hypotonic saline is within normal limits, and the white cell count is usually low with a relative lymphocytosis. Increased red cell destruction is manifested by the usual indications of a raised icteric index and increased excretion of urobilinogen. That the red cell destruction is intravascular is shown by the presence of hæmoglobin and of met-hæmalbumin (Fairley, 1941).

The condition is not hereditary and is usually first noted between the ages of twenty and forty On the whole it is commoner in males than in females.

The pathological changes differ from those in familial acholuric jaundice in that they are indicative of intravascular rather than intracellular hæmolysis. The spleen is enlarged and its sinusoids are dilated, but siderosis is not marked. The liver is usually enlarged and shows central zone necrosis. The kidneys also tend to be enlarged and display marked siderosis. Venous thrombosis is a frequent finding (Scott *et al.*, 1938).

Recent work both in this country (Dacie *et al*, 1938) and in America (Ham, 1937, 1939; Ham and Dingle, 1939) has thrown

Hæmolytic Anæmias

As liver and iron therapy supplemented by blood transfusions resulted in no sustained improvement, splenectomy was decided upon. This operation was performed by Professor J. R. Learmonth thirty-two days after the patient's admission to hospital. Gall-stones were found during the operation, but in view of the patient's condition the gall-bladder was not interfered with. The patient stood the operation very well but subsequently developed a urinary infection which responded to sulphonamide therapy. The patient's condition deteriorated, however, in spite of repeated blood transfusions, and death occurred thirty-eight days after the operation.

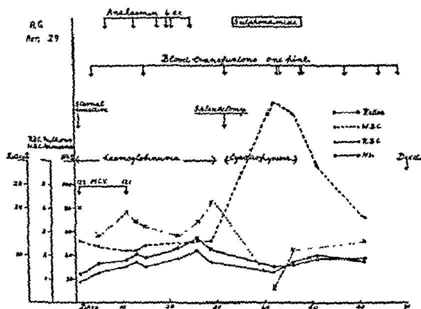


FIG. 1.—Showing course of case of nocturnal hæmoglobinuria.

It is significant that hæmoglobinuria was not detected after the operation.

The spleen weighed 260 G. and histological examination revealed dilatation of the sinusoids with thickening of the reticulum framework. The Malpighian bodies were not enlarged and histiocyte hyperplasia was not apparent. Free iron was present

A saline extract of the freshly minced spleen tissue was examined for the presence of hæmolysins against the patient's red cells, with negative results

Permission for autopsy unfortunately was not obtained.

been diagnosed and treated with injections of liver extract, which were continued for three years at monthly intervals and then stopped. The patient continued in fairly good health, but stated that his complexion had long been sallow, and that he had suffered periodic attacks of epigastric pain and vomiting. Recently he had noted that his urine was often dark in colour.

There was no significant family history.

Physical examination revealed marked pallor, slight jaundice, but fairly good nutrition. The tongue was not atrophied. The spleen was just palpable, but no enlargement of liver or lymph glands was detected.

Laboratory findings: Wassermann negative; icteric index 15; Van den Bergh positive indirect; urine, albumin in small amounts, but no casts, urobilin was present in excess, hæmoglobin was present but no red cells or bilirubin. Free acid was present in the resting gastric juice.

Blood examination: hæmoglobin 24 per cent., red cells 985,000 per c.mm., colour-index 1·2, M.C.V. 122 c.μ., reticulocytes 20 per cent., white cells 2600 per c.mm. Anisocytosis and macrocytosis were marked. *Platelets were present in approximately normal numbers. Red cell* fragility in hypotonic saline was consistently normal.

Sternal puncture revealed a cellular marrow with normoblastic erythropoiesis.

The bleeding and clotting times were within normal limits.

A number of experiments were performed with the object of demonstrating hæmolysis *in vitro*. The patient's washed cells were exposed to his own serum and to the sera of normal individuals of the same blood group, both with and without the addition of guinea-pig complement, and both with and without preliminary chilling. In no case was hæmolysis observed during periods of eighteen hours at room or at incubator temperature Similar experiments in which normal cells were exposed to the patient's serum were also negative. The effect of varying the *p*H of the mixtures was also tried Slight hæmolysis was observed in mixtures of approximately *p*H 6·5. A more significant result was obtained with the simple test described by Dacie *et al* (1938), in *which the patient's heparinised blood displayed hæmolysis after standing a few hours in a tube layered over with paraffin in* order to prevent loss of CO_2. Control tubes containing normal blood or the patient's blood without the paraffin layer showed no hæmolysis.

The progress of the patient is shown in the chart. During the first month in hospital hæmoglobin was regularly present in both morning and evening urines, but on six occasions on which rough quantitative determinations were made the pigment was more abundant in the morning urines. Met-hæmoglobin, urobilin and traces of albumin were also regularly present, but casts, red cells or pus cells were not found during this period.

Paroxysmal Hæmoglobinuria, also known as hæmoglobinuria e frigore, has long been known to be precipitated by exposure to cold. It is probably always associated with a congenital or acquired syphilitic infection and is due to the production of a lysin which at reduced temperatures may cause sudden intravascular auto-hæmolysis.

The presence of the hæmolysin in active or latent cases may be demonstrated by the well-known Donath-Landsteiner reaction (for review see Mackenzie, 1929).

Burns.—Anæmia apparently due to intravascular hæmolysis may result from severe burns. It has been suggested that it may be produced by absorption of protein cleavage products having hæmolytic properties (Whitby and Britton, 1942)

Bacterial Infections.—Since certain pathogenic bacteria such as *Cl. welchii*, *Staphylococcus aureus* and *Streptococcus pyogenes* are capable of producing powerful hæmolytic exotoxins, it is not surprising that infections with these organisms may result in intravascular hæmolysis. Gas gangrene infections are particularly prone to cause severe hæmolytic anæmia which may be accompanied by hæmoglobinuria (Hill, 1936; Fairley, 1941).

Snake Bite.—Bites inflicted by snakes belonging to the colubrine family may result in hæmolytic manifestations. Mention has already been made of the lyso-lecithin mechanism of cobra venom (Kellaway, 1939)

3. *Hæmolytic Anæmias due to Parasitic Infections*

Malaria is by far the commonest cause of hæmolytic anæmia. The anæmia is usually moderate in degree and normocytic in type with a persistent reticulocytosis, and is accompanied by hyperbilirubinæmia and increased urobilinogen excretion.

Although intravascular destruction of the red cells by the parasites would seem an obvious explanation of the hæmolysis, it is not at all certain that this is the chief mechanism since hæmoglobinæmia and met-hæmalbuminæmia are not usually found (Fairley and Bromfield, 1933; Fairley, 1941) The absence of free hæmoglobin in the plasma may be explained by its fixation in the cells of reticulo-endothelial system, and to a limited extent by its conversion within the parasitised corpuscle into malarial pigment (Heilmeyer, 1933) It is considered by Fairley (1940b), however, that the site of red cell disposal in chronic malaria is mainly intracellular, the hypertrophied reticulo-endothelial system

2. *Hæmolytic Anæmias due to Circulating Hæmolysins*

Transfusion Incompatibility.—The dangers of transfusing incompatible blood are now widely recognised. It must be remembered that the use of group O blood provides no guarantee of safety, since, if the iso-antibodies present in such blood be of a high titre, they may cause lysis of the recipient's cells should these belong to a group other than O. Patients suffering from certain types of hæmolytic anæmia are especially liable to such reactions, since their corpuscles may be unduly susceptible to lysis (Dameshek and Schwartz, 1940).

Reactions may also result from the development of "cold agglutinins" in the recipient's plasma. This phenomenon occurs relatively frequently in certain types of hæmolytic anæmia Transfusion of such cases should be done with warm blood previously matched at body temperature.

Rhesus Antibody.—The wide publicity given to the Rh. antigen since its discovery in 1940 (Landsteiner and Wiener, 1940) renders its detailed discussion unnecessary.

The antigen, so named because of its presence in monkey red cells, is also present in the cells of 85 per cent. of normal human beings (Landsteiner and Wiener, 1941). The transfusion of such Rh. positive blood into a Rh. negative individual belonging to the remaining 15 per cent. of the population may lead to the formation of homologous antibodies. If such an immunised individual subsequently be transfused with Rh. positive blood a hæmolytic reaction may result.

The possibility of such a reaction occurring in Rh. negative recipients who require repeated transfusion may be obviated by using Rh. negative blood, or by direct matching performed by an experienced worker using a special technique

Similar immunisation may occur in a pregnant woman herself Rh. negative whose fœtus contains Rh. positive blood inherited from an Rh. positive father

Not only may such a mother suffer a hæmolytic reaction should she subsequently be transfused with Rh. positive blood, but her child's cells may undergo lysis as the result of the maternal Rh. antibodies passing back through the placenta into the fœtal circulation. *This is the current explanation of the grave hæmolytic anæmias of the newly born which have long been recognised* under such names as icterus neonatorum gravis, erythroblastosis fœtalis and hydrops fœtalis (Levine *et al.*, 1941).

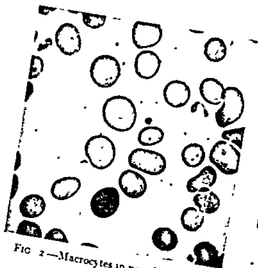
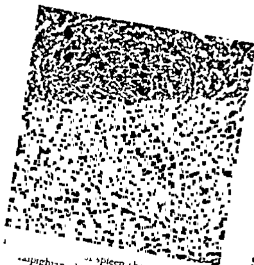


Fig 2 —Macrocytes in peripheral blood. ×720



Fig. 3 —Marrow smear showing normoblastic erythropoiesis. ×720



…of spleen showing atrophied …alpighian body and dilated sinusoids ×90

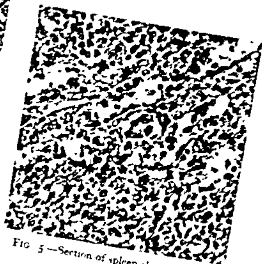


Fig 5 —Section of spleen showing dilated sinusoids ×360

Case of Nocturnal Haemoglobinuria

being responsible for phagocytosing and disposing of the parasitised red cells.

Occasional cases of acute malarial anæmia, however, may show hæmoglobinæmia and transient hæmoglobinuria indicating undoubted intravascular hæmolysis. Such a case was seen last year in Edinburgh.

The malnutrition and worm infestations that commonly complicate malaria may influence erythropoiesis, resulting in the blood picture being often hypochromic and sometimes macrocytic. It is also probable that the malarial infection may itself exert a depressant action on erythropoiesis, since the institution of antimalarial therapy may result in a temporary rise in the reticulocyte count (Fairley and Bromfield, 1933).

Oroya Fever.—In animal pathology a considerable number of parasites are known to attack the red cells with resulting hæmolysis. In human medicine, however, apart from the four species of malaria parasite, the only other red cell parasite is *Bartonella bacilliformis.* It is not settled whether this organism should be classified among the protozoa, bacteria or rickettsia. It is established, however, as the cause of Oroya fever or Carrion's disease, an acute and serious hæmolytic anæmia confined to the western slopes of the Andes. The parasite is transmitted by biting insects such as the sand-fly.

4. *Hæmolytic Anæmias due to Certain Poisons*

Lead is perhaps the best known of the poisons that may cause destruction of red cells. While acute hæmolytic anæmia is a rare finding in lead poisoning, a mild anæmia with evidence of blood regeneration is common. It must be remembered, however, that individuals vary in their susceptibility to the toxic effects of lead. The increased hæmolysis is attributed to the cells being rendered brittle by an action of lead on their surfaces (Aub *et al.*, 1925). The fragility of the cells in hypotonic saline is decreased, however. The characteristic punctate basophilia results from the basophilic material of the reticulocytes being modified by the lead (Whitby and Britton, 1933) The anæmia is usually hypochromic and microcytic, although macrocytosis has been described (Davidson, 1932).

Certain hæmolytic poisons such as phenylhydrazine exert a direct lytic action on the red cells; but the mode of action of many of these poisons is obscure. It should be noted that a

...de of poisons capable of causing extensive hæmolysis may act directly on the bone-marrow and result in aplastic anæmia.

Phenothiazine is included in the list since its use has recently been advocated in the treatment of threadworm infestation (Manson-Bahr, 1940), but cases of severe hæmolytic anæmia have been attributed to its administration (Johnstone, 1942).

Promin, recently introduced in the treatment of certain forms of tuberculosis, is prone to cause hæmolysis (Hall *et al.*, 1942).

3 Hæmolytic Anæmias due to Hypersensitivity to Drugs or Other Agents

Sulphonamide Anæmia.—The sulphonamide drugs have been placed under a separate heading since it is probable that the hæmolytic manifestations that may follow their administration result from an idiosyncrasy or sensitivity on the part of the patient. The mechanism of hæmolysis, however, is unknown. The complication is uncommon, for the great majority of patients receiving large doses over long periods show no evidence of hæmolysis. On the other hand, when it does occur it appears early, within 2-5 days from the commencement of administration of the drug, and often after only moderate doses. Moreover, the susceptibility of sensitive individuals has been shown to persist over periods of at least a year (Fox and Ottenberg, 1941).

The anæmia has usually been reported as normocytic but may be macrocytic (Jones, 1943). The hæmolysis is presumably intravascular since met-hæmalbuminæmia and hæmoglobinuria have been reported (Myers and Rom, 1940).

Most of the sulphonamide preparations commonly employed, such as sulphanilamide, sulphapyridine and sulphathiazole have been reported to cause occasional hæmolytic anæmia, but I am not aware that sulphadiazine or sulphaguanidine have yet been incriminated.

Fabismus, or *favismo*, is a condition peculiar to Southern Europe, particularly Sardinia, where thousands of cases are said to occur annually (Luisada, 1941). It is characterised by the sudden onset of intravascular hæmolysis resulting in hæmoglobinuria and a severe anæmia.

The onset of the disease is related to ingestion of the seeds or inhalation of the pollen of the bean *Vicia faba*, which is grown in abundance in the localities concerned, and accordingly it is

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thought to be due to sensitisation to the plant. Since these beans are grown in many other parts of the world it would appear likely that some additional ætiological factor is involved.

Baghdad Spring Anæmia.—A similar syndrome affecting children and having a seasonal incidence was described in Baghdad by Lederer (1941), who considered that the condition resulted from acquired sensitivity to the pollen of certain flowers.

6. *Hæmolytic Anæmias of Unknown Cause but with Known Predisposing Factors*

Blackwater Fever is an acute hæmolytic anæmia accompanied, as its name implies, by hæmoglobinuria and by other manifestations of intravascular hæmolysis.

It is now generally accepted that the onset of blackwater fever is conditioned by a chronic infection with subtertian malaria. The nature and mechanism of the precipitating factors, however, still await discovery

Among the many theories that have been propounded, a recent suggestion by Fairley (1940b) merits consideration. According to this theory a lysin or enzyme produced in the cells of the reticulo-endothelial system is responsible for the normal destruction of red cells. The prolonged stimulus to the reticulo-endothelial system of a chronic malarial infection results in an increased production of this lysin, so explaining the mild type of malarial hæmolytic anæmia already referred to. It is suggested that under certain unknown conditions the hyperplastic reticulo-endothelial system may suddenly liberate large amounts of the lysin into the circulation and thus precipitate an attack of blackwater fever. The fact that no such lysin has ever been demonstrated in the plasma in cases of blackwater fever is explained by its immediate fixation to the red cells

Macgraith et al (1943b) have recently observed that the anti-hæmolytic effect of normal serum is depressed in blackwater fever and suggest that this may be a pertinent factor in its ætiology, while Foy and Kondi (1943) have reported increased fragility of the red cells to lyso-lecithin.

In blackwater fever the degree and rate of hæmolysis may be extreme, with resulting severe anæmia, azotæmia and massive hæmoglobinuria.

Anuria is a common cause of death as in other forms of intravascular hæmolysis.

It has usually been believed, since the work of Baker and Dodds (1925), that such anuria results from precipitation of acid hæmatin in the kidney tubules. Administration of alkaline salts has accordingly been widely popularised as a preventive measure in conditions where intravascular hæmolysis is occurring or likely to occur. De Navasquez (1940) produced experimental evidence throwing considerable doubt on the rationale of alkalisation, and Foy *et al.* (1943) have recently reviewed the whole question of anuria and conclude that its chief cause is hæmo-concentration They state, furthermore, that not only is there insufficient evidence for the belief that alkalisation is effective in preventing or relieving oliguria and anuria due to intravascular hæmolysis, but that its adoption may lead to the development of alkalæmia and impairment of renal function, although the reaction of the urine may remain acid

It would appear, therefore, that in the treatment of hæmoglobinuria emphasis should be placed on the correction of dehydration by an ample fluid intake, and the correction of anæmia, where it is severe, by blood transfusions.

In the treatment of established anuria good results have been obtained by ureteral catheterisation and pelvic lavage Benefit has also recently been claimed for the simpler procedure of massaging the ureteric openings per rectum and the kidneys and ureters from the outside of the body (Flynn, 1943)

Symptomatic Hæmolytic Anæmias—It is well known that neoplastic disease is frequently accompanied by a hypochromic anæmia, and that a macrocytic anæmia may result from involvement of the stomach, while a leuco-erythroblastic blood picture may follow invasion of the bone-marrow. It is, however, perhaps less widely recognised that a hæmolytic anæmia may also occur

Hæmolytic anæmias have been reported in cases of carcinoma (Waugh, 1936), Hodgkin's disease (Davidson, 1932), ovarian teratoma (West-Watson and Young, 1938), leukæmia and liver disease (Watson, 1939), reticulum cell sarcoma, syphilis and tuberculosis (Thompson, 1936).

The term symptomatic hæmolytic anæmia has recently been suggested by Singer and Dameshek (1941) to embrace hæmolytic disorders showing an ætiological relationship to underlying morbid processes such as those just enumerated.

Four examples of this type of hæmolytic anæmia have come under personal observation during the past year, details of which will be published elsewhere

The underlying morbid processes were carcinoma of the tail of the pancreas, reticulosis (2 cases) and subleukæmic leukæmia.

In common with several similar cases recorded in the literature (Davidson, 1932; Parkes-Weber and Schwarz, 1934; Watson, 1939), the blood picture in the first two cases was macrocytic and in none of them was there evidence of increased fragility in hypotonic saline. In certain reported cases, however, microspherocytosis and increased fragility have been recorded (Singer and Dameshek, 1941).

The mechanism of hæmolysis in these cases is obscure. In conditions such as leukæmia and reticuloses disturbance of the bone-marrow may result in the production of abnormal red cells having impaired survival values. Such an explanation is, however, obviously unacceptable in cases where hæmolysis is secondary to conditions such as carcinoma with no evidence of bone-marrow involvement. There are no grounds for believing that red cells are destroyed in the tumour tissues. Possibly the neoplastic process may stimulate the reticulo-endothelial cells to erythrophagocytic activity.

The relative infrequency of excessive hæmolysis in all the pathological conditions mentioned raises an obvious difficulty in explaining the nature of the underlying mechanism.

March Hæmoglobinuria results from abnormal blood destruction, but since it seldom causes a significant degree of anæmia it is doubtful whether the condition should be classed as a hæmolytic anæmia.

The disorder manifests itself as a paroxysmal hæmoglobinuria occurring in otherwise healthy young adult males following severe exercise. Such individuals lose their susceptibility after a variable period of months or years. Gilligan and Blumgart (1941) have shown that during attacks the hæmolysis is intravascular but that there is no evidence of persistent increased blood destruction. It seems probable that a postural defect has some bearing on ætiology, since the correction of lordosis by wearing a suitable plaster jacket during exercise was found to prevent hæmoglobinuria

The mechanism of hæmolysis is unknown. The suggestion of Witts (1936) that the hæmolysis may occur locally in the renal vessels is rendered unlikely by the subsequent observation that the hæmoglobin passed in the urine during an attack is only a relatively small proportion of the total hæmoglobin liberated in the plasma (Gilligan and Blumgart, 1941).

The disorder is rare, only about 40 cases having been reported, but it may be less uncommon than this would suggest, since minor degrees of hæmoglobinæmia have been observed in normal individuals after intense and prolonged exercise (Gilligan and Blumgart, 1941).

7. *Hæmolytic Anæmias of Unknown Cause*

Acute Hæmolytic Anæmias.—Since Lederer (1925) described 3 cases of acute hæmolytic anæmia of unknown origin characterised by recovery following blood transfusion, over 70 similar cases have been reported in the literature.

The cases usually display the features of pyrexia, leucocytosis, moderate splenic enlargement, and are often accompanied by gastro-intestinal symptoms A severe anæmia, which may be macrocytic, normocytic or microcytic, rapidly develops. Microspherocytosis and increased red cell fragility may or may not be present (Dameshek and Schwartz, 1940). Jaundice and other signs of increased blood destruction are evident Occasionally hæmoglobinuria occurs (O'Donoghue and Witts, 1932). Children and adults of varying ages may be affected

Although such cases had been described long before Lederer's description, there has been a tendency in the later literature to class them as a clinical entity under the designation of " Lederer's anæmia." This is to be deprecated, since various cases of acute hæmolytic anæmia display significant differences in their hæmatological and clinical features

The desirability of critical scrutiny of all possible ætiological factors is well exemplified by the experience of Murray Lyon (1935), who described 2 cases of acute hæmolytic anæmia developing simultaneously in two brothers One of these cases was typical of so-called Lederer's anæmia, but the other resembled a hæmolytic crisis of acholuric jaundice Subsequent inquiry revealed a family history of acholuric jaundice In the light of these findings it is highly probable that the first case was an unusually acute manifestation of familial acholuric jaundice

The mechanism of hæmolysis probably varies in different cases. In some an acute infection has been thought to be a significant factor Dameshek and Schwartz (1938a) have detected auto-hæmolysins in cases studied by them

The majority of reported cases were cured or improved by blood transfusions but a number derived no benefit. Trans-

fusions should be performed with considerable care, since transfusion reactions are relatively common in these cases.

Splenectomy has been enthusiastically advocated by Dameshek and Schwartz (1940), who consider that the operation should be performed forthwith in all cases showing no apparent benefit after not more than four transfusions. According to an analysis of reported cases made by these authors, transfusion resulted in recovery in 44 of 66 cases, while splenectomy was curative in 20 of 23 cases, most of which had previously been transfused without permanent benefit.

Subacute and Chronic Idiopathic Hæmolytic Anæmia.—Under this heading is included a group of heterogeneous cases in which the anæmia usually first manifests itself in middle life in the absence of any known predisposing cause or familial association, and runs a subacute or chronic course. The acute relapses not uncommonly seen in these cases, however, may render it difficult at times to distinguish them from the acute types just referred to.

In the past many authors have been content to designate this type of case as acquired acholuric jaundice, thus stressing its resemblance apart from the absence of family history and the late age of onset, to the classical familial type. Scrutiny of case reports, however, reveals in many instances significant differences.

An analysis has been made of 47 cases apparently belonging to this group that have been described in the British and American literature since 1932 (Davidson, 1932; Lovibond, 1935; Thompson, 1936; Kremer and Mason, 1936; Duthie, 1937; Davidson and Fullerton, 1938; Dyke and Young, 1938; Israels and Wilkinson, 1938; Mandelbaum, 1939; Fairley, 1941; Fowler, 1941; Sharpe and Tollman, 1942).

In making such an analysis it was necessary to exclude a number of cases not strictly of idiopathic origin, since authors not uncommonly designate as acquired hæmolytic anæmia cases that in this lecture are grouped under the heading of symptomatic hæmolytic anæmia. In spite of this precaution it is possible that cases may have been included that more thorough investigation would have assigned to other categories such as nocturnal hæmoglobinuria. Another difficulty attending an analysis of this kind is the absence in published reports of uniform criteria for the description of hæmatological and pathological features. However, subject to such qualifications, the following conclusions have been drawn.

Of the 47 cases, 33 showed macrocytosis, and of these 18

displayed increased red cell fragility. Microspherocytosis with increased red cell fragility was recorded in only 4 cases. In 3 cases intravascular hæmolysis was indicated by the presence of met-hæmalbuminæmia or hæmoglobinuria. Splenomegaly was a constant finding. The histology of the spleen was reported in 27 cases, but only in 9 was it said to be characteristic of familial acholuric jaundice.

It is evident that the majority of cases reviewed differed fundamentally from familial acholuric jaundice. A residuum of cases remains, however, which does appear to resemble the latter condition apart from the lack of family history. One such case first developed symptoms at the age of seventy-five (Mandelbaum, 1939). Dawson (1931) and others have expressed doubt whether an acquired form of acholuric jaundice exists, arguing that the manifestations in early life may be so slight that they escape notice or are forgotten, and that the so-called acquired cases are probably aberrant forms of the familial type. Davidson and Fullerton (1938) dispute this contention on the grounds that adequate investigation of many such cases occurring amongst a static population failed to reveal any evidence of a familial element.

The prognosis of this group of idiopathic cases is difficult to establish on a statistical basis since many of the published reports do not include adequate follow-up data; but it is manifest that for the group as a whole the prognosis is grave and the mortality rate high.

Treatment.—Blood transfusions are likely to be of only temporary benefit, but should always be tried. All due precautions should scrupulously be observed, since in this group reactions are far from uncommon. The transfusion of serum or plasma is a safer procedure in difficult cases, and may possibly be of value, since it has been shown by Besredka (1901) and Josephs (1938) that serum may exert an anti-hæmolytic effect under experimental conditions. Dameshek and Schwartz (1940) have stated it to be of clinical value.

The question of splenectomy is a vexed one Some authors claim good results in cases belonging to this group, while others are far from enthusiastic. In the 47 cases already referred to, 30 splenectomies were performed; 13 of these were said to result in varying degrees of improvement, 7 failed to influence the course of the anæmia, while in the remaining 10 cases the operation was considered to be the immediate cause of death

It is apparent that splenectomy can in no sense be regarded

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Finally, I wish to acknowledge my indebtedness to the clinicians already mentioned for permission to report the cases under their care, and to Professor L. S. P. Davidson for his ever ready help and advice

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as a routine treatment in idiopathic hæmolytic anæmia, but its advisability must carefully be considered in each individual case after thorough clinical and laboratory study.

It is possible that splenectomy may be more successful in the type of case displaying hæmatological affinities to classical acholuric jaundice than in the type with macrocytic red cells of normal fragility. For it is of interest to note that of 18 cases with increased red cell fragility in which splenectomy was performed, improvement was claimed for 12, while of the 12 cases with normal fragility only 1 was improved by the operation.

It has been pointed out by Haden (1941) that on theoretical grounds splenectomy is unlikely to be of benefit in conditions where hæmolysis is intravascular, unless it be assumed that a diffusible lytic agent may emanate from the spleen. Since there are no convincing grounds for such an assumption, evidence of intravascular hæmolysis may well be interpreted as a contra-indication in cases where the question of splenectomy is under consideration.

Cooley's or *Mediterranean Anæmia* is a rare condition almost exclusively limited to young children of Southern European stock. Commencing insidiously in infancy it runs a progressive course to a fatal termination. The anæmia is generally considered to be hæmolytic in origin, although manifestations of marked hæmolysis may not be evident Normoblasts and reticulocytes are numerous in the peripheral blood, and a frequent finding is decreased fragility of the red cells in hypotonic saline apparently due to the presence of thin bowl-shaped "target-cells." In the later stages of the disease splenomegaly is marked and bone changes involving the cranium may result in a mongoloid appearance.

Examination of close blood relations of affected children has revealed the presence of target cells and decreased fragility (Smith, 1943). It would accordingly seem that the disease is familial and that it might appropriately be classed with other hæmolytic anæmias due to an abnormality of the erythron.

A similar but milder variant of this condition has recently been described in adolescents and adults (Wintrobe *et al.*, 1940; Dameshek, 1943).

In conclusion to this outline, it is hoped that in some small way it may serve to emphasise the desirability of recording detailed studies of individual cases of different types of hæmolytic anæmia if our knowledge of this interesting group of disorders is to be advanced.

THE TREATMENT OF CEREBRO-SPINAL FEVER BY SULPHAPYRIDINE

By ALEXANDER JOE, *D.S C*, M.D., F.R.C.P.Ed.

SINCE its first appearance in epidemic form in this country in 1907-8 until 1936, spinal puncture and drainage, combined with the intrathecal injection of anti-meningococcal serum, had become the accepted method of treatment of cerebro-spinal fever. In the latter part of this period, however, workers became dissatisfied with their results, the earlier relative successes obtained with the use of the Flexner serum by Ker in Edinburgh, where the hospital mortality was reduced from 80 to 37 per cent., and by Robb in Belfast, being no longer forthcoming, and more intensive methods of administration were devised with the object of improving the outlook, which was now generally regarded as highly unfavourable. Thus large quantities of concentrated serum were given intravenously, intraperitoneally, and intramuscularly, while access to the cerebro-spinal circulation was sought by cisternal and ventricular as well as the earlier method of lumbar puncture. Such intensive treatment was carried out every twelve hours by some, and various workers claimed by these methods to show improvements in limited series of cases. On the other hand, many with considerable experience could claim no particular benefit by the adoption of these intensive methods, and from my own observations on 50 cases seen in 1932-1934 at the North-Western Hospital, London, I came to the conclusion that they represented no advance on our previous practice, the case fatality being exactly 50 per cent.

Edinburgh experience was even less favourable. Thus of 383 cases treated in the City Hospital from 1920-37 inclusive, a few of which received almost negligible doses of sulphonamide in the last few months of that period, the case fatality was 68·7 per cent., and during the period mentioned it will be acknowledged that the treatment was according to the highest standards. It may be said, therefore, that until the introduction of the sulphonamide group of drugs the prospects of recovery in cerebro-spinal fever continued to be precarious. Before returning

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evident that there would be an opportunity for an exhaustive clinical trial of sulphapyridine. It was decided, therefore, to continue with this drug until a reasonable volume of evidence had been accumulated on the subject. During the course of our work one or two other drugs were introduced which offered attractive possibilities, and I was greatly tempted to run parallel series of cases treated by these as well. Since, however, really conclusive results cannot be obtained in an investigation of this type unless there is treated a large number of cases in which each age group is adequately represented, I decided to put these aside until I was satisfied that some definite appraisal of the value of sulphapyridine could be made. I am now in a position, therefore, to present the results of treatment in 500 consecutive cases of cerebro-spinal fever by this substance. This is the largest series reported on by a single observer up till the present so far as I know.

The 1940-41 Epidemic

Before proceeding to analyse the results it is necessary to give a short account of the epidemic, and for this purpose I have prepared a table of the monthly admissions of proved cases to the City Hospital in 1939, a year which represents the ordinary experience of the hospital in non-epidemic periods, together with those of the epidemic years of 1940 and 1941. It will be noted

TABLE I

	Jan.	Feb	Mar	Apr	May	June.	July	Aug	Sept.	Oct.	Nov.	Dec.
1939	1	3	1	1	1	1	1	1	1	2	1	2
1940	18	72	68	34	29	23	11	13	16	8	15	13
1941	19	33	33	31	19	13	14	6	3	9	11	6

that in January 1940 there was a sudden increase in the number of cases, rising to unprecedented heights in February and March and then falling slowly in the second quarter, but during the second half of the year maintaining a relatively high monthly admission rate. In 1941 we had a repetition of the events of the previous year although on a reduced scale. This seasonal incidence conforms generally with previous records, which show that the late winter and spring months are the periods of maximum prevalence, sharp spells of cold weather, such as occurred in the

to Edinburgh in 1937, I had had the opportunity in 1936 of treating 3 cases of cerebro-spinal fever with the original prontosil rubrum. This was combined with the intensive serum therapy then practised, but all three patients succumbed, and accordingly I was a little sceptical of the favourable reports following the use of this substance which began to appear in the journals. However, during the later months of 1937, as opportunity offered, treatment with various preparations of the sulphonamide group was combined with serum, sulphanilamide, proseptasine and soluseptacide being the chief drugs then available. At first these were given orally, and by intramuscular and intraspinal injection, but a short experience soon convinced me that the new drugs were dangerous when given by the last-mentioned route, so that this method was quickly given up. When later the intrathecal administration of serum was also abandoned, there was a marked improvement in the mortality rate, and for the first time in my experience I began to obtain a substantial recovery rate in infants of less than twelve months, in whom previously a recovery was a somewhat rare event. Serum was still given intramuscularly and intravenously, but encouraged by our own observations and those of others, the important step was taken of finally abandoning serum, reliance now being placed on oral and intramuscular administration of suitable compounds At this stage an already confused situation was not rendered less difficult by the flood of proprietary preparations of the sulphonamides which were put on the market. Much of the controversy as to the most suitable compound and the method of administration was brought to a conclusion during the summer of 1938 by the advent of sulphapyridine, which became generally available. Results with this substance were most favourable, the first twelve consecutive cases in which it was employed at the City Hospital all recovering. This was a finding quite outwith the range of all previous experience with serum treatment upon which our knowledge of the progress of the disease had been founded. In clinical severity and age distribution the cases were similar to those seen in the past, and moreover the fact that the signs and symptoms together with the cerebro-spinal fluid cleared up within four or five days in all, pointed definitely to the drug as the sole factor which determined this remarkable change. These results, not of course uniformly favourable, but showing a considerable improvement on those obtained in the past, were maintained throughout 1939, so that when the epidemic of 1940 broke upon us it became

is met by the argument that it is in the early years of this group, *one to five*, that the case fatality is high, and accordingly the necessity for pressing the drug, within the limits of safety, is very great. In those over twelve, treatment was begun with an

TABLE II

Scale of Dosage

Day	1.	2	3	4	5	6.	7.	8.	9.	10.
12+ years	12	12	6	6	3	3	3	1·5	1·5	1·5
1-12 years	6	6	3	3	1·5	1·5	1·5	0·75	0·75	0·75
0-1 years	3	3	1·5	1·5	0·75	0·75	0·75	0·75	0·75	0·75

intravenous injection of 2 gm., and in those between one and twelve with a similar injection of 1·0 gm. of soluble sulphapyridine. Thereafter the total daily amount was divided into two-hourly doses given by mouth for the first forty-eight hours, and in four-hourly doses for the second forty-eight hours. Subsequently the drug was given three times a day until the end of treatment. In infants the initial intravenous dose was omitted, the drug being given orally from the beginning, two-hourly for the first forty-eight hours, four-hourly for the second forty-eight hours, and three times a day thereafter. For oral administration the tablets were crushed in milk The main obstacle to giving the drug by the mouth was, of course, vomiting, one of the cardinal signs of the early stage of the disease, and when this interfered with treatment recourse had to be made to intravenous and intramuscular injection until vomiting was brought under control In stuporose patients, or in those in whom marked opisthotonos interfered with swallowing, the drug was given by the nasal tube, and that this was effective was shown by the fact that patients treated in this way for three or four days have proceeded to complete recovery Apart from lumbar puncture for diagnostic purposes, I have given up repeating this process except in cases which seem to hang fire, and in younger children for reasons which will be mentioned later. When chemotherapy was first begun, daily lumbar puncture was carried out; later this was done every other day, and finally when it was realised that the yield of a clear sterile fluid under normal pressure corresponded exactly with the disappearance of signs and symptoms by the fourth to

early weeks of 1940 and 1941, being frequently followed by increased incidence. The sex distribution of the 500 cases considered was also typical in that males outnumbered females, 270 against 230. Broadly speaking, the age incidence was also characteristic in that the chief prevalence was in children under five, 33·4 per cent. of the patients falling into this category. It must be pointed out, however, that after middle life the incidence was somewhat higher than usual. The normal expectation is that cases are uncommon at this age period, but in my series 12 per cent. were over forty years of age. Anomalies of this type are almost bound to occur when age incidence is calculated in a relatively limited population such as that served by the Edinburgh City Hospital. In its general features, therefore, the epidemic did not differ from those experienced in the past. In one respect, however, it was unique, namely, its magnitude. As far as the Edinburgh City Hospital is concerned, all previous records were broken, and for some weeks we never had less than 80 cerebro-spinal fever patients in the wards at one time. The diagnosis was confirmed by the finding of meningococci in the cerebro-spinal fluid in all but a few cases. The lack of bacteriological proof in these few was the result in every instance of sulphonamide treatment having been initiated before the arrival of the patient in hospital, but in view of the characteristic clinical signs they were admitted to the series. The meningococcus was cultured from the cerebro-spinal fluid and typed in 128 cases in the Department of Bacteriology of the University, 116 cases showing a Group I, and 1 case a Group II organism. The remaining 11 were unclassifiable by the type serum available. Owing to pressure on the medical staff we were unfortunately unable to perform blood culture as a routine

Dosage and Method of Administration

On the basis of previous experience, an arbitrary scale of dosage was laid down at the outset of the epidemic, and this has been adhered to throughout as shown in Table II.

Compared with that employed by other workers the dosage is high, especially at the outset of treatment, but it was felt that as long as these doses were tolerated the greater the amount that could be given the better. The criticism that a wider range of dosage for the various age groups might have been advisable, and this is especially the case in the one to twelve age period,

Taking the sulphapyridine treated group first, it will be seen that the case fatality is high in the first five years of life, drops in the second quinquennium, disappears altogether in the second decade, rises again between twenty and forty, until it reaches its maximum in the fifth and subsequent decades. To those with much experience of cerebro-spinal fever in the pre-chemotherapeutic era, the most striking feature of these results is the complete absence of fatal cases between ten and twenty years, and a more detailed analysis at the various yearly periods shows that among 107 patients aged eight to nineteen years not a single death occurred. When we recall the pathology of the condition this can only be regarded as remarkable. Again, taking all cases, 261, between the ages of eight and thirty-nine we have the moderate fatality of 4·2 per cent. I would like it to be clearly understood, moreover, that in compiling these tables every death occurring in any patient admitted with proved cerebro-spinal fever is included in the table. Some amplification of this point is perhaps necessary. In the first place 21 out of the 90 fatal cases were noted as moribund on admission and died within twenty-four hours of arrival; in fact more than half died in less than eight hours. In their presentation of results some have claimed the exclusion of such cases on the ground that the method of treatment was being set an impossible task. In cerebro-spinal fever, however, we must keep in mind the fulminating variety of the disease, just as much a case of cerebro-spinal fever as any other, and if the picture is to be complete all such must be included. It is not suggested that all 21 were of the fulminating type, as some had been ill for as long as eight, nine or ten days, but approximately half could be so classified. With another group of 6 fatal cases included in the series we are on more debatable ground. Of these, a female of seventy-four died on the seventeenth day of illness of coronary thrombosis verified by post-mortem examination; 3 children died of acute gastro-enteritis on the twenty-first, twenty-fifth and twenty-seventh day of illness in circumstances which suggested an intercurrent ward infection; and 2 from whose cerebro-spinal fluid Group I meningococci were cultured on admission, but who died of proved pneumococcal meningitis on the thirty-sixth and forty-ninth days after the onset of the cerebro-spinal fever. At post-mortem no evidence of meningitis was found in the coronary thrombosis and gastro-enteritis cases, and it would probably be logical to exclude them. The succession of a meningococcal by a pneumococcal infection

the sixth day, repetition of puncture as a routine was discontinued. Cisternal and ventricular puncture have practically passed out of use in treatment. Until chemotherapy has done its work I have not hesitated freely to prescribe full doses of morphine or morphine and hyoscine compound to control delirium and relieve the excruciating headache. Abundant fluids were given also. Various drugs such as nicotinic acid have been recommended to render the sulphapyridine more tolerable to the patient, but I have always returned to McLean's alkaline powder as the most helpful. Many patients complain of acute gastric pain when recovery has set in, and whether this is due to the irritant effect of the drug or the stress of continuous vomiting is difficult to say, but it usually yields to a few doses of chlorodyne.

Results on Case Fatality

The results of chemotherapy in terms of case fatality at the various age periods, the most searching of all the tests which can be applied to any new method of treatment, are set forth in the subjoined tables, and for the purposes of comparison they are given in parallel with those obtained in all cases treated by serum at the City Hospital during 1920-37.

TABLE III

Comparison of Case Fatality Rates in Cerebro-spinal Fever by Age Groups from 1920-37 and 1939-41

	Age Group.	0-1.	1-4.	5-9	10-14	15-19	20-29.	30-39.	40-49.	50+.	Total
1920-37	Total . .	128	97	31	26	28	38	10	8	8	383
	Died . .	111	67	16	11	13	20	12	6	7	263
	Percentage died	87	69	52	42	46	53	63	75	87	68·7
1939-41	Total . .	64	115	45	43	57	63	53	15	45	500
	Died . .	17	30	4	..		3	4	8	24	90
	Percentage died	27	27	9·0	Nil	Nil	5	7	53	58	18

TABLE IV

Percentage Distribution of Cases in above Table according to Age Groups

	0-1.	1-4	5-9.	10-14	15-19	20-29.	30-39	40-49.	50+	
1920-37	33·4	25·3	8·1	6·7	7·3	9·9	4·9	2·1	2·1	99·8
1939-41	12·4	23	9	8·3	10·7	12·3	10·3	3	9	100

characteristic rash, of whom there were 201, had a poorer chance of survival than those without, the percentage case fatality of the two groups being 21·4 and 15·6 respectively. The day of disease on which treatment was commenced was also of some effect on the end result, though the statistical evidence on this point is not so clear as could be desired. The table submitted shows that

TABLE V

Case Fatality Rates According to Day of Disease on which Chemotherapy commenced

Day	1	2	3	4	5	6.	7.	8	9	10	10+.	Total
Cases	24	66	116	59	57	32	21	9	8	1	17	410
Deaths	2	14	27	20	5	6	5	4	1	2	4	90
Total	26	80	143	79	62	38	26	13	9	3	21	500
Per cent. of total	7 6	17·5	18 8	25·3	8 0	15 8	19 2	30 8	12 5	66 6	19·0	18 0

when sulphapyridine was given on the first day the results were better than those obtained when treatment was begun on subsequent days up till the fourth The results in patients receiving treatment for the first time on the fifth day, however, are almost as good as those when treatment was begun on the first, and the number of cases coming under treatment at this time is sufficient to enable us to come to a reasonable conclusion. I think also it can be said that, except possibly in infants, the date of onset in cerebro-spinal fever is not difficult to establish, so that the histories obtained in individual cases are not likely to be far out. Possibly in the fifth-day group we are dealing with cases in which the onset was less acute, and the initial signs and symptoms being less well marked, medical aid was sought late. Another point worth keeping in mind in this connection is that as untreated cases of cerebro-spinal fever may proceed occasionally to spontaneous recovery, any group coming late into hospital would be likely to contain a number in whom natural recovery had already commenced. Conversely, the overwhelmingly severe infections, in which any kind of treatment was not likely to succeed, would be concentrated among those receiving treatment in the first two or three days.

is interesting; all who have any extensive acquaintance with cerebro-spinal fever have probably encountered one or two such cases which in the past have given rise to much heart-searching over the bacteriological identification of the causal organisms at the outset of the illness and over the technique of spinal puncture. Whatever opinion may be as to the inclusion of these various fatal cases in the series, this explanation makes it clear that the figures given are no understatement of the case fatality rates.

Comparison with Serum Therapy

To gain a true perspective of the advance made by chemotherapy a comparison with the results obtained by the use of serum is necessary. From the comparative tables submitted it will be seen that in addition to the great reduction in the total case fatality at all ages, from 68·7 per cent. in the serum treated to 18 per cent. in the sulphapyridine treated cases, this reduction has operated in all age groups. It is particularly noticeable in the first quinquennium, and more striking still in the first year of life. Whilst not so well marked in the 40+ age group, chemotherapy has made an impression even there, whilst in the intervening years the difference in case fatalities is remarkable. It is essential to make the comparison by age groups because case fatality in this disease has always varied according to age, and a contrast between the total fatalities at all ages in any two series is quite inconclusive unless this important variable is given full weight. Indeed the two case fatalities now given are not strictly comparable, because in the serum treated group a much higher proportion of the patients, 33·4 per cent., fall into the particularly vulnerable first year of life as compared with 12·4 per cent in the sulphapyridine group (See Table IV.) On the other hand, the sulphapyridine series is disadvantaged by the relatively high proportion of patients in the 50+ group, 9 per cent, as compared with the 2·1 per cent. in the serum treated.

Other Factors affecting Fatality

Other factors affecting fatality in the sulphapyridine treated cases are sex, presence or absence of rash, and day of disease on which treatment was commenced With regard to sex, of the 270 males 40, or 15·9 per cent, died, whereas of the 230 females 47, or 20·4 per cent., died. Again, patients showing the

In order to avoid such an event as occurred in the first-mentioned case, I decided to check up on the clinical condition by lumbar puncture in a series of children under five a few days before dismissal from hospital. Our results were interesting in that over a period of about two months we encountered 5 patients who appeared clinically to be in a most satisfactory condition, but although the cerebro-spinal fluid was crystal clear and not under pressure, scanty meningococci could be demonstrated microscopically, and in one instance a type 3 organism, the same as the original infecting strain, was isolated on culture. In all cases a short course of sulphapyridine was given, and this was followed by a disappearance of the meningococci This routine has been continued ever since, but in not a single case has this experience been repeated. While *herpes* can hardly be regarded as a complication of cerebro-spinal fever, it appears so frequently as a concomitant that some mention of it requires to be made. It occurred in 18·4 per cent. of our cases, usually on the fourth to the seventh day of illness, but was seen as late as the thirteenth. Commonly on the lips, it was by no means confined to that situation, and lesions with a zoster distribution occurred on the forehead and cheeks, nose, external ears, on the trunk, and on the limbs. Twice as common in females as in males, it was seen most frequently in the twenty to thirty age groups, and only one patient died who showed herpes. To those who take an interest in such events, it may be stated that in the cerebro-spinal fever wards there were two outbreaks of chickenpox which could not be traced to a primary infecting case of the disease.

With regard to the progress of the disease, in all but a negligible minority obvious recovery was taking place, or death had intervened by the end of the tenth day of disease, 84·4 per cent of the deaths occurring within that period. Cases passing into the subacute stage were few, 8 in all, and usually lumbar puncture followed by another course of sulphapyridine quickly had the condition under control. In the whole series only 1 case developed spinal block and *hydrocephalus* resulting in death. Once convalescence was established, patients rapidly returned to normal, although in a proportion of adults recovery seemed to be marred by persistent headache, often described as a dullness, worst in the morning, and passing off during the day. By the time they had left hospital at the end of four or five weeks this had disappeared in all but a few, but I have information of several cases in which the condition has remained for months

Complications in Sulphapyridine Treated Cases

Turning to complications, *arthritis* occurred in 21 or 4·2 per cent. of all cases and was the most frequent. Over one-third of the patients suffering from this were in the twenty to thirty age group, and it seemed to be slightly commoner in males. Usually single joints were involved, but multiple joint lesions were not unusual, and arthritis was often accompanied by myositis and tenosynovitis. In the order of frequency of involvement were the elbow, shoulder, knee and ankle. The condition appeared in the second week of the disease, and in practically all cases yielded to simple physiotherapy and a further short course of sulphapyridine. In one patient, however, an ankylosis of the left shoulder joint resulted *Neuro-labyrinthitis* resulting in nerve deafness was the next commonest complication, 10 examples, or 2 per cent. of all the cases, being seen. Half occurred in the ten to fifteen age period, and 5 were bilateral and 5 unilateral The loss of hearing was complete in the affected ear or ears in 6 of the patients on leaving hospital, 2 having cleared up and 2 having been only partially affected from the first; but 1 patient, who on discharge was stone deaf, spontaneously recovered within a period of three months. Other residual phenomena were *squint* in 5 cases, *ptosis* in 1, and *facial paralysis* in 3. *Neuritis* occurred in 9 cases, or 1·8 per cent., but in only 2 did this result in prolonged disability: in 1 case a drop foot which is still showing no signs of improvement, whilst in the other the ulnar nerve was involved. In the early days of treatment some speculation was made as to whether neuritis might be a toxic effect of the drug, but later 2 patients, admitted late, showed the complication before sulphapyridine had been administered *Irido-choroiditis* occurred in only 1 of our patients. It appeared in the first week of illness, and although a very bad prognosis was given by the ophthalmologist who saw the patient, the condition cleared up rapidly as the sulphapyridine was continued, leaving a normal eye with normal vision. In the only 2 pregnant women in the series *abortion* occurred, and both patients made uncomplicated recoveries. *Relapse* occurred in 2 cases. Both had received the usual course of treatment and 1 was returned to hospital with unmistakable signs of cerebrospinal meningitis within forty-eight hours of discharge. The other showed a return of signs and symptoms in the third week. Both responded quickly to a further full course of sulphapyridine.

phenomena such as *digestive disturbances* and *depression* were difficult to assess. *Vomiting* I have already referred to as one of the cardinal signs of the disease, and it was impossible to decide how much this was a manifestation of the disease and how much it resulted from sulphapyridine in the early stages. If, however, the drug was persevered with it was remarkable how the vomiting disappeared, and this alone was not a deterrent to its use as has been the case in my experience with sulphapyridine treatment in some other conditions, such as pneumonia. Many patients complained of *nausea*, but with encouragement they managed to retain the drug. A sense of *fullness in the epigastrium*, *flatulence*, and *epigastric discomfort* and *pain* were frequent, but 'this usually disappeared with the progressive reduction in the dose. *Mental depression* was also often marked, and some patients have referred to this as almost the worst feature of the whole illness. *Blood changes*, which have now been reported in many conditions treated by sulphapyridine, did not come to my notice, apart from an occasional leucopenia which was relatively transient. Deep *sterile abscesses* resulting from the intramuscular injection of soluble sulphapyridine are undoubtedly a drawback to the employment of this method. They take a considerable time to heal and delay convalescence, but in certain cases the risk must be taken, otherwise the use of the most effective remedy for the disease will require to be abandoned. In any case, when the precaution advised by the makers is taken of diluting the drug in solution with three times its volume of sterile saline the occurrence of abscesses is not very common. Taken all over, and considering the large total amounts of the drug which were given, I saw no toxic effects which could be held to be serious contra-indications to its employment. Indeed, it is not too much to say that cerebro-spinal fever patients tolerated sulphapyridine very much better than any other class of patient to whom I have found it necessary to give the drug.

Discussion of Results

From this account it will be realised that we have for the treatment of cerebro-spinal fever a most effective substance in sulphapyridine, which in its action shows all the hall-marks of a specific remedy in the true sense of the term. Like all specific remedies, it only required to be employed in a few cases for its value to be immediately apparent, and the question at once

and has been accompanied by a lack of power of concentration. Several patients have also complained of stiffness of the legs for a month or two after leaving hospital.

Toxic Effect of the Drug

Some account of the side effects of the drug as seen in this disease is now necessary. *Rashes* were relatively common and were encountered in 35, or 7 per cent, of the cases. They were more often seen in males (8·1 per cent.) than females (5·6 per cent.), and 24 out of the 35 were distributed over the five to thirty age period. Twenty-one occurred on the ninth, tenth or eleventh days of treatment, and this interval between onset and time of appearance rather suggests an etiology similar to that of serum rashes. They appeared as generalised erythemata on the face, trunk and limbs, and almost invariably were morbilliform or rubelliform in character. The resemblance to the rashes of measles and rubella was so close that at times the diagnosis was most difficult, and indeed in the early days of the use of the drug, before we had some acquaintance with drug rashes, I made the diagnosis of measles with some confidence, isolated the cases and took the usual precautions. The position was further complicated by the fact that pyrexias of 100° or 101° F. were usual with the rash, and occasionally some facial œdema occurred as well. Indeed, apart from the absence of Koplik's spots and catarrh, which after all may be absent in mild attacks of measles in adolescents and adults, there seemed to be very little on which to make a distinction, although later an urticarial element may predominate in the rash and give the clue to the condition. *Drug fever* as a sole effect of the drug was also relatively common, but as it is not always possible to exclude with certainty other causes for an elevation in temperature, I have not attempted to estimate the incidence of this Usually disclosed by a sharp rise in temperature lasting from two to four days, it may be indicated by a niggling pyrexia lasting for a week and be accompanied by general malaise and depression. Infants often become exceedingly irritable *Urinary complications* were only encountered in 4 cases, all males, and consisted of temporary anuria in 1 case, albuminuria in 1 case, and hæmaturia in 2 cases. Two occurred on the seventh day, and two on the ninth day of the administration of the drug, and with its prompt withdrawal and the giving of abundant fluids they cleared up in a few days. *Subjective*

as far as therapeutic effect is considered, while others have published excellent results with sulphathiazole and sulphadiazine. The question also arises whether we could improve our results still further by a combination of serum and drug therapy. My personal opinion is that in the inter-epidemic years the results of serum-therapy were so unimpressive that I doubt if anything is likely to be gained by the combination. Nevertheless there are theoretical grounds for believing that the efficiency of the drug could be increased in this manner. That there is room for improvement admits of little argument. The great progress recently made should not blind us to the fact that in certain age periods the fatality of cerebro-spinal fever is still high, and whether this will yield to further advances in the chemical field, or whether the essential pathology of the condition will present a barrier to progress, it is impossible to say. The work of Banks and J. E. McCartney indicating the existence of an encephalomyelitis in addition to a meningitis is significant in this connection, as this would appear to impose limitations on what we can expect from treatment. Lastly, are the results, such as they are, as good as they appear to be, or are there remote residual effects in patients recovered from the acute phase after chemotherapy? Clinicians have looked anxiously for these, and probably some have occurred, but I doubt if they have to any great extent, otherwise we would have heard of them by this time, as after all it is more than two years since many of the recovered patients have resumed their ordinary activities. In the meantime I think we have cause to be grateful for our recent progress There can be no doubt that with the introduction of the sulphonamide drugs we have witnessed remarkable developments in the treatment of infectious diseases. In none has their administration had more spectacular and convincing success than in cerebro-spinal fever.

Thanks are due to my former residents, Drs McQueen, Osroff and Doreen Stevenson, for assistance in the preparation of the statistical material embodied in this paper

arises as to whether the results set forth in this paper are superior to those obtained on the introduction of the Flexner serum which inspired such great hopes. Even assuming the initial success with serum was as great as that now obtainable with the drug, it must be admitted that, for whatever reason, *e.g.* change of type of infecting organism or the like, it was not lasting, whereas, if the current theory on the mode of action of the drug on bacterial metabolism is correct, there should be little doubt that the present advance will be maintained and possibly extended. We are led from this to another question discussed by some of the older clinicians who gained their first experience of the disease in the 1907-08 epidemic, namely, whether during the recent epidemic we were dealing with as virulent a type of infection as was experienced at the time. One at least was of the opinion that we were not, and this point is, of course, of first-class importance in any attempt at comparison of present-day chemotherapy with the serum treatment practised at that time. A reasonable conclusion in the matter will never be possible, since it is axiomatic that any real assessment of the merits of different types of treatment of infectious disease can only be made if the results of treatment by these methods in a parallel series of cases in the same epidemic are analysed What can be said, however, with fair certainty is that the form of the disease encountered in the recent epidemic was definitely not less severe than the sporadic forms seen in 1920-40, and which we have seen carried a fatality of 68·7 per cent. in Edinburgh. As far as I am able to judge, therefore, the striking results of chemotherapy have not been due to any recent waning in severity of the disease Other points remain to be discussed. It will have been noted from the results of typing the organisms isolated from a fair proportion of the total number of cases that the epidemic was almost entirely a Group I infection Is sulphapyridine likely to be as effective in Group II infections? In all probability this will prove to be the case, and in the few Group II infections of which I have had experience, the results have been comparable with those in Group I, but it might be well to await further information on this point Then, again, is it possible to say that sulphapyridine is the best drug for the treatment of cerebro-spinal fever? The only other which I have used to any extent, sulphanilamide, did not appear to approach sulphapyridine in rapidity or certainty of action, but some whose judgment I respect do not believe there is much to choose between the drugs

as air movements, the presence of men and animals and their activities. As might be expected, bacteria are most numerous in the air of populated places, particularly within enclosed premises and more especially ill-ventilated crowded places. On the other hand, free ventilation of occupied premises lessens the tendency to an abnormally high bacterial content. Fig. 1 illustrates the rising bacterial content of the air in an insufficiently ventilated air-raid shelter occupied for several hours.

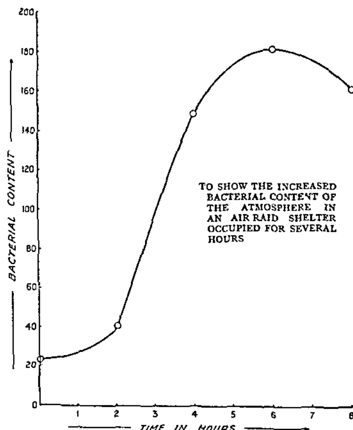


Fig 1.

It is of academic interest that at high mountain altitudes and over deserts the air is comparatively free from bacteria, while over the sea the number increases with proximity to the shore, but as evidence of the widespread dispersal of bacteria, not even the

THE PROBLEM OF AIR-BORNE INFECTION

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SINCE the times of Hippocrates when fires were lit in the streets of Athens to purify the air and arrest the plague, there has been a firm belief that the atmosphere is a source or vehicle of disease. At the beginnings of bacteriological science Pasteur's studies on fermentation, Lister's discoveries in wound infection, and Tyndall's observations on the floating matter of the air, seemed to provide the biological justification of these earlier ideas; but it soon emerged that the air contained for the most part harmless saprophytic organisms, and the problems of air bacteriology after occupying a most prominent position in hygiene about the end of last century were later relegated to an unimportant place in medical literature. In fact, the theory of air-borne infection was almost abandoned. In recent years, however, aerial infection has been restored to its earlier prominence, and at the moment certain problems of war-medicine have focussed the closest attention on this subject. The present time is therefore opportune for reviewing critically our knowledge of the subject and evaluating new contributions to it.

For such review we must consider first certain fundamental facts The atmosphere is not a natural habitat of micro-organisms; nevertheless fungi and bacteria are almost invariably present in the air. These emanate from various substrates in which they flourish; in short, from the earth's surface and its human and animal inhabitants. Particles of dust from the soil, streets, public places, dwellings, etc., stirred by air currents and all the movements incidental to human and animal life, dried material shed from the surface of the body of man and animals, and droplets of moisture expelled from the respiratory passages create the apparent microflora of the atmosphere.

So many different factors contribute to the occurrence of aerial micro-organisms that it is not surprising to find great numerical variation in time and place. Anything which increases suspended particles of dust and droplets adds to the bacterial content, such

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to it from their natural habitats, and in the second place can withstand the drying influence of the atmosphere. It has been long recognised that the pathogenic bacteria vary in this respect, some being resistant, others susceptible. It might therefore appear that from our knowledge of the viability of these organisms and their mode of access to the outer world we should be able to say which infections are air-borne and which are not. This interpretation, however, is not so simple as it might seem. Studies of the resistance of bacteria to drying have often yielded diverse results according to the conditions of desiccation. Natural air-drying of cultures may cause rapid death, but most bacteria, if dried from the frozen state *in vacuo* and kept *in vacuo*, retain their viability for long periods. This method, in fact, is utilised as a means of preserving live bacterial cultures. Our knowledge of the influence of the different conditions under which desiccation may occur is still incomplete. Moreover, dust particles may only be partially dry, and if they contain any hygroscopic material may retain sufficient moisture to preserve the viability of associated bacteria. Factors which would determine the survival of bacteria in dried matter are the nature and volume of the material, the temperature, humidity, whether the air is still or subject to movement, and the age of the bacterial units (see Gotschlich, 1927-29). Strains of the same organism may also vary greatly in their susceptibility to drying.

Since Koch's historical work it has been accepted that the tubercle bacillus among the non-sporing bacteria can resist natural desiccation. Cornet (1889), who strongly upheld the theory of dust transmission of micro-organisms, found living tubercle bacilli in desiccated sputum and in the dust of hospital wards and rooms occupied by phthisical persons. It has been generally agreed that this organism remains viable in dried material for months if protected from light, though when exposed to sunlight it dies rapidly, even within a few hours. The prolonged survival of the bacillus in the dry state has, however, been questioned. Kirstein (1905) stated its survival in dust as eight days only, when exposed to diffused light. Cadéac (1905, 1908) claimed that the organism dies about the sixth day after drying, so that by the time a sputum becomes pulverisable the tubercle bacilli have died and cannot therefore be distributed by air.

The susceptibility to drying of a variety of pathogenic organisms was first studied systematically by Germano (1897), and it is interesting to note that while he found the typhoid

stratosphere is bacteriologically sterile (see W. F. Wells and M. W. Wells, 1936; Proctor, 1934, 1935).

While bacteria enter the air often in large numbers their stay may be a comparatively short one. As dust particles and droplets settle by gravity, the contained organisms are removed from the atmosphere and the rate of removal will depend on the size of the particles, the larger tending to settle rapidly, the smaller remaining suspended for an appreciable time and also diffusing, as it were, for some distance. Deposition occurs more quickly in a quiet atmosphere than a disturbed one. On the other hand, air currents within an enclosed space by causing particles to impinge on a surface to which they can adhere tend to reduce the bacterial content of the atmosphere. Humidity also causes a diminution of bacterial content by coating dust particles with moisture, and by inhibiting evaporation of droplets so that they settle more rapidly. It is stated further that high humidity causes small particles to adhere into larger and heavier aggregates.

The apparent microflora of the air comprises mainly spores of various fungi, spores of the aerobic bacilli, *e.g. Bacillus subtilis* and allied organisms, and a variety of micrococci, *e.g.* saprophytic staphylococci and sarcinæ. Some of these organisms are specially adapted biologically for air distribution, as is well exemplified by the fungi whose spore-bearing hyphæ offer the fruits of their reproduction to the air currents which carry them off to new breeding grounds. Such spores are also resistant to the desiccating influence of the atmosphere. Sporing bacteria are distributed in nature in a somewhat analogous manner; their spores, however, are not reproductive but are well adapted for survival under adverse conditions as in air and dust, provided they are not exposed to direct sunlight. Thus, air samples regularly contain these bacteria, which are prevalent inhabitants of soil and decomposing material. But many non-sporing bacteria can also survive to a greater or less degree in desiccated material and are found in air and dust. While mould spores may occur as free structures in the air, bacterial spores and bacterial cells depend for their distribution in air on the drying and pulverisation of the material in which they occur naturally or on the spraying into the air of fluids in which they may be present As Flügge (1897) pointed out, bacteria are not lifted by air currents from moist surfaces.

It may be said that the micro-organisms most likely to be found in the air are those which, in the first place, can gain access

In assessing the practical significance of an organism's survival in dust, we must judge in the long run by the finding of that organism in the dust of places where it is being discharged from the bodies of infected persons. The occurrence under these conditions of pyogenic staphylococci and streptococci, the pneumococcus, virulent diphtheria bacilli and tubercle bacilli is well authenticated by both early and recent work (see Cruickshank, 1935; White, 1936; Allison and Brown, 1937; Hare, 1940; van den Ende and Spooner, 1941; H. D. Wright *et al*, 1941). The observations of Avery and his co-workers (1917) on the occurrence of pneumococci in dust are of special interest. They frequently found the common epidemic types (I and II) in the dust of wards with pneumonia cases, whereas in ordinary rooms the commensal types were more prevalent. The poliomyelitis virus was demonstrated by Neustadter and Thro (1911) in the dust of a room occupied by a case.

In the early studies of aerial infection the historical work of Flügge (1897) on "droplet" infection tended to minimise the importance attached to dust transmission, and his work has dominated our ideas of air-borne infection up to the present time. He claimed that the essential mechanism of transmission of bacteria from the respiratory tract of an infected person is by the secretion droplets expelled in the act of sneezing, coughing and speaking. Thus, even organisms which are sensitive to drying, such as the meningococcus, if introduced into the air in droplets of secretion which remain suspended, may rapidly enter the respiratory passages of other persons in the vicinity and so spread the disease. Under these conditions resistance of an organism to drying is not primarily essential for spread. But, as Chapin (1916) has pointed out, such droplet infection might more properly be regarded as a form of mediate contact infection rather than true air-borne transmission.

Normally, expired air is free from the organisms present in the respiratory passages, but forced expiration with its spray of secretion causes the introduction into the air of large numbers of bacteria from the respiratory tract. Flügge (1897 and 1899) carried out experiments in which the mouth was artificially infected with *B. prodigiosus*, and observed that in coughing the organisms were immediately carried 9 metres from the mouth (see also Laschtschenko, 1899) Flugge held that the droplets float in the air for five to six hours and can be transported by air currents of 1 mm per second. Leon (1903-4) estimated that

bacillus survived for months when dried in clothing, this organism died rapidly in dust, which illustrates the conditioning of survival of organisms in dried material. From his general observations he concluded that such infections as cholera, plague, typhoid and gonorrhœa could not be dust-borne.

There has been general agreement that pathogenic staphylococci and streptococci are resistant to drying. Kurth (1891), for example, showed that streptococci survived for five to seven weeks in the dried state. Kirstein (1902) sprayed cultures of *Streptococcus pyogenes* on fine particles of dust and found the organism remained alive for ten days in diffused daylight. According to Wood (1905) the pneumococcus survives for about thirty days in dried sputum in diffuse light. Germano (1897*c*) found the organism alive after 120 to 155 days in dried sputum mixed with dust. The diphtheria bacillus has been long regarded as resistant to drying. Recently Crosbie and Wright (1941) have found that this organism may survive for three months in infected dust exposed to moderate light. They have also recovered the living organism from the floor of a ward after a month.

It may be accepted from all the evidence available that among the pathogenic bacteria which may readily gain access to dust under natural conditions and may be distributed by dust in the air, the following can survive in the dry state for a significant period: the tubercle bacillus, staphylococci, streptococci, pneumococcus, diphtheria bacillus, spores of the anthrax bacillus (in wool factories), spores of anaerobic bacilli (*B. tetani*, *B. welchii*, etc.) and the spores of various pathogenic fungi. It is possible also that under certain conditions organisms of the *Brucella* group may be distributed in dust Bacteria which cannot withstand drying for an appreciable period are the gonococcus, meningococcus, Pfeiffer's bacillus, *B. pertussis*, *Vibrio choleræ*, and *B. pestis*. Further, it seems unlikely that the typhoid bacillus and other *Salmonella* organisms, and the dysentery bacilli are distributed naturally by dust (see Cowan and Mackie, 1919).

Many of the viruses have considerable resistance to desiccation, and when discharged from infected persons would be able to survive in air and dust. This is well exemplified by the viruses of smallpox, vaccinia, psittacosis and poliomyelitis. The last-mentioned virus has been found still active in dried material after twenty-four days (Landsteiner and Levaditi, 1911). Recent work has also shown how the influenza virus can survive in dried material for weeks if protected from light (Edwards, 1941).

certain earlier workers. Thus, Le Noir and Camus (1908) found that when tubercle bacilli could be demonstrated in the dust of a hospital ward, they could not be detected even in as much as 53,000 litres of the air of the ward. Fig. 2 (curve of natural

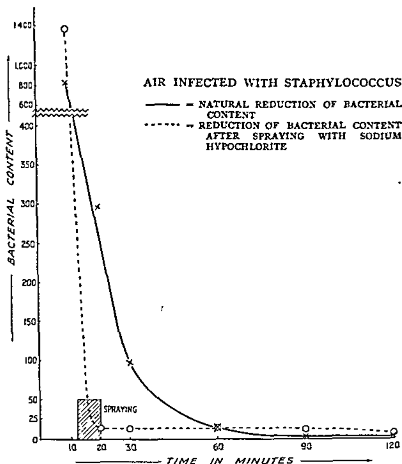


FIG. 2.

reduction of bacterial content) shows how rapidly air is cleared of organisms introduced in a watery spray consisting mainly of large droplets. The organism used for the test was *Staphylococcus albus*, an organism which is resistant to drying. Though the number detectable in the air was initially very large, there was a rapid decline within thirty minutes, and by sixty minutes the air was practically cleared.

in speaking 300 words a person expelled about 250,000 bacteria from his mouth (about 800 bacteria per word!). Winslow and Robinson (1910) showed that *B. prodigiosus* may be distributed from the mouth of a speaker throughout a room, but they pointed out that only the smallest droplets remain suspended in the air, the larger particles settling out within a few feet of the mouth.

The later work of Wells (1934) has done much to clarify our knowledge of droplet transmission of bacteria. He showed that droplets of 0·1 mm. diameter or more settle rapidly, but that smaller droplets tend to remain suspended. The latter, however, evaporate, giving place to "nuclei" of dried material, and these "droplet-nuclei" float for a considerable time in the air and can also be carried some distance by air currents. Such nuclei are, in this respect, like smoke particles which may persist in air for hours or even days. If a pathogenic organism remains viable in droplet nuclei, the potential spread of the infection would be very great indeed. Here again the resistance to drying of individual pathogenic species would be a determining factor. The larger droplets containing most of the organisms from the respiratory passages would immediately contribute to the bacterial content of the dust of the premises, and the smaller ones would directly contaminate the air, while in the course of time the bacteria in the droplet nuclei, when they finally settle, would add a further quota to the bacterial contamination of the dust. If such organisms survive and the dust is stirred, they would again temporarily contaminate the air.

To summarise: the larger droplets settle rapidly and the resulting bacterial contamination is localised and concentrated in the particular area; smaller droplets become floating particles of dried residue, but the bacterial contamination produced by them is diffuse and also dilute. The still more recent work of Hare (1940) has added further knowledge to this subject. He studied the emission of secretion droplets from streptococcal carriers by arranging exposed plates of blood-agar in a semicircle with the mouth as the centre, and found that hæmolytic streptococci were expelled only in small numbers and were contained mainly in the large droplets which at once fall to the ground. His findings would suggest that these organisms are not so frequently transmitted from person to person by secretion droplets or droplet-nuclei, but rather by contamination of dust, and the later stirring of the dust into the atmosphere. Hare's work emphasises dust as opposed to droplets, a view taken by

particles directly into his respiratory passages; moreover, the smaller particles remaining in suspension and being carried by air currents may be inhaled by others at some distance within the same premises—not necessarily the same room but also communicating rooms.

The question arises as to the actual demonstration of pathogenic organisms in the air, as apart from the dust, of premises containing cases of particular infective diseases. The demonstration of the tubercle bacillus and of hæmolytic streptococci under these conditions may be accepted. Pathogenic staphylococci can be detected in air samples from places occupied by normal persons, and this is not surprising in view of the frequency of these organisms on the surface of the body and in the nose and throat But in such demonstration of pathogenic organisms in samples it must be remembered that the organisms may be derived from suspended dust particles as well as from droplets or droplet-nuclei.

Certain writers have suggested that even if an organism survives in air or dust, the drying to which it is subjected and the exposure to light will so affect its vitality and virulence that a few such devitalised organisms introduced into the body are easily destroyed by the natural defences and are unable to cause pathogenic effects. Noeggerath (1900-1) referred to this in connection with the aerial contamination of wounds. We cannot deny the likelihood of such devitalisation; on the other hand, virulence is not necessarily lost by drying as has been demonstrated by the finding of virulent strains of tubercle and diphtheria bacilli and of streptococci in dust. Thus, van den Ende and his co-workers (1940) have shown that virulent hæmolytic streptococci may be derived from beaten blankets even after four weeks.

In all such studies of air-borne infection the technique of examining the air bacteriologically is of primary importance The simplest method has been to expose open plates of appropriate culture medium for a given time. The organisms settling on the medium form colonies on incubation and so a qualitative and quantitative examination can be made. This method has proved quite useful for detecting such organisms in air as hæmolytic streptococci. Counts made by this means are, of course, only of comparative value

More elaborate methods have also been used, but these need not be referred to here. A new technique, however, introduced

W. F. Wells and M. W. Wells (1936) have defined the viability of various organisms in droplet-nuclei, and the comparative survival is more or less as stated earlier. Streptococci, pneumococcus, *B. diphtheriæ* and *B. subtilis* persist for over two days. Pfeiffer's bacillus dies within one hour. The virus of epidemic influenza was found viable for at least one hour after introduction into the air.

Though sedimentation of solid or liquid particles and their adhesion to surfaces undoubtedly tends to clear the atmosphere, there is nevertheless a remarkable diffusion of bacteria when bacteria-containing droplets are introduced into the air. Trillat (1938) showed that a *B. prodigiosus* culture sprayed into the keyhole of a room spread a distance of 17 metres in two minutes. It is of interest that W. F. Wells and M. W. Wells by inoculating, the humidifying water of an air-conditioner in the basement of a three-storey building, found the organisms were dispersed throughout the whole building. In a large public air-raid shelter in Edinburgh, taking 500 persons and divided up into 13 compartments, it was found that even a coarse spray of *B. prodigiosus* culture at one point led to diffusion of the organisms practically throughout the shelter and into each compartment, this diffusion occurring within five minutes. Throughout the shelter the organisms were still settling from the atmosphere after sixty minutes, and at points distant from the place of spraying more organisms settled out between thirty and sixty minutes than during the first thirty minutes. The shelter at the time was empty and there was fair ventilation in the corridors and some of the compartments

Among the variables that determine air distribution of bacteria is the very important one of the vigour of expulsion of droplets from the respiratory passages, and sneezing is the most effective in this respect. A photographic technique has been devised by Jennison (1941), and applied also by others for studying the spray from the mouth and nose. Bourdillon and his co-workers (1941) found that an average sneeze leads to the emission of 100,000 bacteria-containing particles of a size small enough to remain in the air of a closed room for more than one minute, and that 4 per cent. of these particles remain suspended in still air for thirty minutes.

Sneezing is undoubtedly the most fruitful means of distributing respiratory tract organisms and viruses in the air. Another person in the immediate vicinity is bound to take some of the

reported that spacing out of beds beyond this reduced the spread of nasopharyngeal infection by the meningococcus. Another disease attributed to droplet infection and overcrowding in cold climates and seasons is pneumonic plague. Kitasato (1911), however, pointed out that it was air-borne only at close quarters. It seems clear that this also is an instance of "direct" or "immediate" droplet infection. According to Wu Lien Yeh (1922), transmission is only effective within a range of 3 feet. In the case of whooping-cough, Biernacki (1908) stated that if beds in a hospital are spaced out to 12 feet to prevent immediate droplet infection there is no spread. Of course the organisms of these diseases are not resistant to drying.

What is the possibility of air-borne infection at long range? At the time of the 1889-90 pandemic of influenza it was even suggested that this infection was wafted across the Atlantic (see Leichtenstern, 1905), but trans-oceanic spread of disease requires a more substantial vehicle than *air!* At one time smallpox was said to be carried by air from infectious diseases hospitals to neighbouring populations, but this idea was based probably on fallacious epidemiological interpretations. Poliomyelitis has been thought to be dust-borne in the *outer* air, and certain writers have commented on the cessation of new cases after watering of the streets (see Chapin, 1916), but this is not very satisfactory evidence. I will *not* deal with the transmission of excretal organisms such as the typhoid bacillus by contaminated dust or sewer air. Much was at one time written on the subject, but nothing ever proved.

The essential problem *is* the question of effective transmission of specific pathogenic organisms or viruses throughout the air of enclosed premises so that persons breathing the air of the place contract the disease, and wounded tissues exposed to such air become actively infected.

The bacteriological data indicate that such transmission is possible *in* a number of diseases of the respiratory system or diseases which commence in the respiratory tract, *e g* tuberculosis, pulmonary anthrax, diseases due to hæmolytic streptococci, pneumococcal infection, diphtheria, certain fungal infections, smallpox, the common cold and epidemic influenza. But it is at once clear that the degree of such infectivity of the air will depend on certain simple factors pertaining to ordinary hygiene, *e g.* the state of general cleanliness of the premises, the stirring of dust in various ways, ventilation, the cubic capacity of the place

by Bourdillon and his associates (1941), merits some consideration. This involves the use of an instrument which is designated a "slit-sampler." By this means a volume of air is directed through a narrow slit of given size on to a plate which is rotated mechanically to ensure even distribution of the organisms. It is claimed that by this method the finest bacteria-carrying particles are collected, whereas the simple exposure of plates permits mainly the collection of large particles.

I have now outlined briefly the bacteriological knowledge on which we may base our views regarding air-borne infection, but the final proof must come from epidemiological, clinical and experimental evidence. This is peculiarly lacking in many cases, and it must be remembered that even when air-carriage seems a likely mode of transmission, and we know that this is bacteriologically possible, contact will equally well explain the spread of the particular infection. If it is established, however, that a pathogenic organism is discharged into the air from the respiratory passages of an infected person, if it can survive and retain its virulence in dust, in droplets or droplet-nuclei for a sufficient time to enter the respiratory passages of other persons, and if it is known that this is a successful avenue of infection, there is a strong case for air-borne infection. The longer the organism can survive outside the body the greater will be its striking power and range in time and space.

Many infective diseases are attributed quite categorically to droplet-infection, and no one will question such transfer when a person with the specific organism or virus in his nose or throat sneezes or coughs with his mouth or nose uncovered so that another person or persons in the immediate vicinity inevitably takes into his respiratory tract at once some of the smaller secretion droplets from the infected individual. This applies also to infection from a person with virulent organisms in his mouth or throat who coughs or speaks unmasked or imperfectly masked over an open wound. Whether we are to classify this as air-borne or contact-infection is debatable, but for descriptive purposes we may speak of it as "direct" or "immediate" droplet infection.

The question arises as to the actual striking distance of droplet infection through the air. Epidemiological evidence has shown that in some cases it is a short one. Glover's (1920) work on the spread of meningococcal infection indicated that in this case the distance *in sleeping quarters is only about 3 feet*; he

unnecessary to postulate any other mode of infection than contact. It is of interest to note that Wright and his associates (1941), in a recent study of diphtheria cross-infection in an infectious diseases hospital, have found that this may amount to 10 per cent. in ordinary wards, while it rarely occurs in cubicle wards. Their finding of virulent diphtheria bacilli in ward dust has led them to believe that dust is a source of such cross-infection. In their publication they comment on the influence of old-fashioned methods of sweeping in spreading infection by dust—another factor to be considered in the control of air-borne infection.

There seems to be no satisfactory evidence of true air-borne infection in measles, rubella and mumps, though these are often regarded as transmissible by droplets.

Psittacosis provides a likely example of air-borne infection. Thus, infection without contact has been shown to occur in premises containing an infected bird, and it has been recorded how the virus on one occasion spread throughout a three-storey building probably by the ventilation system (see W. F. Wells and M. W. Wells, 1936).

Smith and Stuart-Harris (1936) have shown how influenza may be contracted from the sneeze of an infected ferret in the vicinity, but this may have been an example of direct droplet infection. We have evidence, however, from the work of Wells and Henle (1941) that influenza may result from exposure to air containing infected droplet-nuclei.

Recent observations by Faber and Silverberg (1941) would indicate that poliomyelitis may be air-borne

Infections by hæmolytic streptococci have received special attention in relation to air transmission. There can be no doubt of the occurrence of cross-infection by these organisms in infectious diseases hospitals and in surgical and obstetrical wards. Thus, in a high proportion of the complications of scarlet fever cross-infection is apparently responsible, the infecting strain being different from that responsible for the primary disease When it was shown that the air of scarlet fever wards contained hæmolytic streptococci the conclusion was drawn that cross-infection was due to dust and air-borne droplet infection. It must be remembered, however, that direct and mediate contact may play a greater part in such infections, and to explain their occurrence it is not even necessary to invoke air-borne infection Apart from scarlet fever, similar infection has been reported in children's

and the number of persons present. The potential infectivity will be greatest in crowded, dirty and unventilated premises. Even good lighting is an inhibitory factor. Thus, satisfactory hygiene of occupied premises must limit air infectivity. As contrasted with some forms of contact infection, air-borne transmission must often imply great dilution, as it were, of the infection.

As regards evidence of effective air-borne infection, a considerable amount of work was done at one time to obtain clear proof of such transmission of tuberculosis. A review of the literature reveals some discordant elements in the story, but studies of this disease certainly offer the best evidence, bacteriological, experimental and epidemiological, of infection borne through the air by dust, droplets and droplet-nuclei. We have no proper knowledge, however, of the striking range, and the danger can only be a serious one when there is absence of what might be regarded as ordinary hygiene. (I am not referring to what I described as "direct" droplet infection.)

There is evidence of the true air-borne character of pulmonary anthrax in wool factories, but the data indicate that the striking range is a comparatively short one.

Petrie (1929) has commented on the fact that a number of bacteriological workers have died of primary pneumonic plague as a result of inhalation of infected material in the laboratory, but points out that insufficient ventilation has been a factor in these cases.

Smallpox, with its myriads of minute virus bodies in the crusted skin lesions which can resist drying, has long been accepted as a possible air-borne disease, but the vast majority of cases could probably be explained as due to contact (see Clayton, 1905; Chapin, 1916). Ker (1920) pointed out, however, that a person entering an ill-ventilated room containing a case of the disease might contract infection, but in this comment again we see the simple hygienic factor illustrated. Sabongy (1923), in fact, questioned from his experience of handling thousands of cases of smallpox whether this virus was air-borne to any extent.

Diphtheria may undoubtedly be spread by direct droplet infection, and the bacteriological data would indicate that in enclosed premises the disease may be air-borne by infected dust, droplets or droplet-nuclei, but we have no definite evidence of this from other sources, and epidemiologically it might seem

cleaners; adequate ventilation; a "quiet" period in the ward before dressings to allow of sedimentation of floating dust resulting from movements in the ward, and particularly bed-making. It has also been pointed out that the dust from bedding can be reduced to a minimum by treatment with paraffin. It has been shown that many of the masks that have been in common use are not effective; the ideal mask should consist of a layer of impervious substance between two layers of gauze and should completely cover the nose, mouth and chin, fitting over these parts in such a way that there is no exit for secretion droplets at the edges (see Medical Research Council Memorandum, 1941). Miles and his co-workers allude to the possibility that a hæmolytic streptococcus from the air may not successfully infect wounds, but that their presence in the air may lead to an infection rather of the respiratory passages where their number becomes, of course, greatly increased; thus the wound is finally infected from the secretion droplets of the patient.

Some years ago special attention was drawn to the production of operative infection by streptococci and other organisms derived from the mouth or nose of surgeons, nurses and others present in the theatre at operations (see Meleney and Stevens, 1926), and of course the universal practice of masking in theatres is a recognition of this danger; but such operative accidents have probably been the result of a direct droplet infection by a highly virulent organism at close range, and they should not be taken as exemplifying true air-borne infection in a theatre The same source of infection has also been fully recognised in relation to puerperal sepsis (Watson, 1928; Meleney *et al.*, 1928; Smith, 1931, Colebrook, 1935) There still remains the question of operative infection from bacteria-containing particles floating in the air of a theatre. It is recognised that even in the best regulated theatres potentially pathogenic staphylococci are present in the air, but all recent surgical experience would show that there is little risk of actual infection of operative wounds unless perhaps in operations of long duration with large areas of tissue exposed and extensive manipulations We must recognise that if only a few organisms gain access to an operative wound, unless of specially high virulence, they are rapidly disposed of by the natural defences.

An interesting contribution to this subject has been made by Hart (1937, 1938), who has reported on the use of a "field of air" for operations, sterilised by bactericidal radiation from

wards, leading to sore-throat, otitis, wound infection, etc., and Wright (1940) has pointed out that cubicle isolation prevents such spread. Of course, prevention of cross-infection by cubicle isolation does not necessarily imply air-borne infection.

The case for air-borne streptococcal infection might seem to be a strong one if we consider the occurrence of the organisms in the air and dust of certain types of ward and their resistance to drying. Allison and Brown (1937) showed that the prevalence of hæmolytic streptococci in ward air was least during the night and high in the morning when active movements and bed-making took place with the stirring of dust from the floor and bedding. These are significant facts in relation to the practical control of such air-borne infection.

It came to light during the war of 1914-18 that wound infection by *Streptococcus pyogenes* was in the majority of cases a hospital infection, and this subject has received most intensive study in the present war. It is, of course, recognised that there are various sources and modes of such infection dependent on imperfections in the technique of wound management, but there has been a tendency to ascribe secondary sepsis in many cases to infection from dust and air. Miles and his co-workers (1940) have reviewed the sources and modes of such air-borne infection. They attribute air-spread to infected droplets from the respiratory passages of patients and hospital personnel and to infected particles derived from dressings, plasters and bedclothes contaminated with wound discharges. Thus *Streptococcus pyogenes* is present in the upper respiratory passages of at least 5 per cent. of the normal population, and potentially pathogenic staphylococci have been found in the nose in 40 per cent. of hospital personnel. Plaster used in the closed method is an abundant source of infected dust. It has been found that plates of medium exposed on beds while wounds are being dressed, or plates exposed during bed-making, yield growths of pathogenic organisms such as *Streptococcus pyogenes*.

Recent work on wound infection has indicated various comparatively simple precautionary methods. These include masking during dressings and inspections, and masking of the patient; the opening of plasters only in a separate room; silence of the patients in the ward during dressings; treatment of floors with spindle oil which creates an adhesive surface with retention of sedimented particles (van den Ende *et al*, 1940); abolition of dry sweeping; dusting with damp cloths; use of vacuum

regards the latter, much will always depend on environmental conditions, ventilation, crowding, stirring of dust, etc., and under good hygienic conditions air-borne pathogenic bacteria may be so dilute as to be ineffective in producing respiratory tract infections or wound infections. Even the danger of short-range droplet infection may be reduced to a minimum by simple precautions—in hospitals by proper masking, in ordinary life by the use of the handkerchief.

Should we take the extreme view that the reality of air-borne infection is minimal, we could not deny that under certain conditions it must occur, and that particularly under such conditions preventive measures are demanded as in infectious diseases hospitals, surgical theatres and wards, crowded premises with inadequate ventilation, especially during periods of prevalence of epidemic diseases. The last is well exemplified by the air-raid shelters of the present war.

Recently, efforts have been made to establish effective means of air disinfection. At present, the most practicable method for ordinary living or working premises is one of chemical disinfection, and towards this end progress has undoubtedly been made. The most promising technique is to introduce into the air a fine spray of a disinfectant which, in the concentration used, will kill pathogenic bacteria without exerting any poisonous or irritant action Various substances have been found to have air-disinfectant properties, *e.g.* certain coal-tar or phenolic derivatives, glycols, incense, smouldering cardboard, etc., but it can be said that a hypochlorite solution yielding hypochlorous acid is at present the most likely choice for practical use It is still controversial whether the chemical acts in the form of very small droplets by its contact with the suspended organisms or whether it acts in a gaseous form (see Twort and Baker, 1940; Dodd, 1940; Andrewes *et al.*, 1940; Twort *et al.*, 1940; Masterman, 1941). Hypochlorite spraying has the merit of being easily applicable and the solution in certain concentrations is known to be bactericidal, non-poisonous and non-irritant An instrument of the flit-gun type suffices for spraying, preferably the baffled gun as recommended by workers at the National Institute for Medical Research.

The efficacy of the method can be clearly demonstrated under strictly experimental conditions, *e.g.* where bacterial cultures are introduced into the air of a room and then followed by a hypochlorite spray, and in this way some indication has been obtained

ultra-violet lamps; and he claims that operative mortality has been halved in this way and operative infection reduced to a tenth. It must be remembered, however, that ultra-violet radiation as a practical means of sterilising the air has considerable limitations. The final solution of the problem has still to be attained, and it must be borne in mind that wound infection may come about in other ways than from floating particles in the air. Virulent staphylococci abound in the nose, and the utmost *perfection of methods of masking is of primary importance.* Moreover, a multitude of staphylococci from the skin of the perspiring hands and fingers may enter a wound through inappreciable punctures of gloves. These sources of infection require perhaps more attention than the dispersed bacteria of the air (see also Devenish and Miles, 1939).

It may be added that Barenberg (1940) has reported a significant reduction in respiratory tract infections as a result of ultra-violet radiation in children's wards, and a reduced incidence of measles, chicken-pox and mumps in a school has also been attributed to such radiation (Wells, Wells and Wilder, 1942). But the question arises whether these results could not be obtained by improved hygiene.

What practical conclusions can be drawn from all these data? Under the ordinary conditions of communal life it might seem impossible to avoid the inhalation of other persons' mouth and throat bacteria, and when it is found that in a hospital ward the air carries pathogenic organisms derived from the respiratory passages of infected patients, the atmosphere might seem to us, as it did to our predecessors centuries ago, to be the vehicle of many diseases. We can certainly accept the view that in a number of infective conditions air-borne infection is a definite possibility, and in some a proved mode of spread; but even in the latter we have no knowledge of the proportionate part played by aerial infection. Thus, all the factors that would determine air-borne streptococcal infection are present in certain wards of fever hospitals and not infrequently in surgical wards of general hospitals, but the actual cross-infection in these environments may nevertheless be due mostly to other vehicles and to contact. Moreover, true aerial infection is in the nature of things a dilute infection. Of course, if we were to classify direct droplet infection as air-borne spread we should then have an instance of an "undiluted" infection, and this must be many times more effective than spread by organisms in diffused floating particles. As

to a high degree, air-borne pathogenic organisms must represent a dilute infection which is not therefore a specially potent one. Simple precautions are capable of further diluting such infection, possibly to the point of rendering it ineffective. If circumstances beyond ordinary control are such as to create a serious danger, we have available certain means of reducing the infectivity of the air, and these should be applied more especially when there is epidemic prevalence of a disease which we know is potentially air-borne.

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of the amount of hypochlorite required for a given volume of air. It may also be said that such effective concentrations are not objectionable to the occupants of the premises. Fig. 2 illustrates the results of an experiment of this kind. It should be added that the result shown has been proved by other experiments not to be due to the water vapour as such introduced in the spray.

It is more difficult to demonstrate efficacy under natural conditions. In this case results have to be judged by estimates of the number of organisms present in a given volume of air of occupied premises before and after spraying. As most of the organisms detected in the usual way are saprophytic and some of these are more resistant to the antiseptic than the air-borne pathogenic bacteria, it is difficult in this way to obtain a true index of the efficacy of the method. Recently an endeavour has been made to measure disinfection by counting only the organisms growing on a crystal-violet blood-agar. These consist of streptococci and Gram-negative diplococci from the respiratory passages, and the question arises whether the streptococcal content of air might serve as an index of air purity on the analogy of the *B. coli* content of water.

By tests in a closed room, the air of which was contaminated by sneezing, Bourdillon and his co-workers (1942) have estimated that all or almost all of the bacteria emitted can be killed in three to four minutes by a 1 per cent. hypochlorite spray (2·1 c.c per 1000 cub. ft. of air), but they admit that certain conditions may interfere with efficacy, *e.g.* low relative humidity or high content of organic matter in the air. Challinor (unpublished observations) has shown how hypochlorite spraying reduces the total bacterial count of an occupied room and also the content of streptococci in a room in which the occupants sneezed or coughed. But it would appear that there is not complete disinfection nor, as might be expected, sustained disinfection after a single spraying. In fact, the duration of the effect seems to be limited to a period of about fifteen to twenty minutes. The effect could be maintained by repetition of spraying at short intervals, but this must undoubtedly militate against the practicability of the method.

In conclusion, it may be said that certain infections are in some cases at least truly air-borne, as apart from direct or immediate transmission by droplets, but such aerial infection is conditioned by environmental factors, most of which should be within our control in hospital practice, and to some extent in ordinary life. It is probable that unless these factors are operative

THE FIRST MONTH OF LIFE: GENERAL SURVEY

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J. M. BALLANTYNE, of Edinburgh, the founder of the ante-natal clinic, is said to have coined the phrase, *neonatal period*. The neonatal period covers the first four weeks, or more accurately the first month of life. This first month of life is crowded with critical problems, and the measure of the importance and danger of these problems is the heavy loss of infant life that occurs at this time. In any medical or statistical study of the neonatal period, it is now agreed that the period of birth must also be taken into account, and that the pathological problems of birth are closely linked with those of the first weeks after birth. For this reason the phrase natal-neonatal period is coming into fashion. The general adoption of registration of still-births (natal deaths) in the leading countries of the world is an important advance which will show the full extent of infant mortality during the natal-neonatal period.

Natal-Neonatal Deaths.—In this lecture a broad survey of the problems of the first month of life (including birth) will be attempted. These problems are in the first place physiological, but the physiological problems are so critical, delicate and insecure that they quickly change to grave and dangerous pathological conditions. This general survey may best begin with some facts and figures indicating the heavy loss of infant life during this period These facts have been long recognised, but they have received more attention recently because in the last two decades there has been throughout the world a great fall in infant deaths throughout the first year, while there has been a much smaller decline in the neonatal period This can be illustrated from the vital statistics of any country that has been successful in lowering its infant death-rate. For example, in New York City, between 1930 and 1938, the infant death-rate (that is for the first twelve months of life) fell from 57 to 38, while the death-rate for the first month showed only a small decline in the same period from 30·5 to 25.

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tions a large series of hospital autopsies will broadly define the main pathological processes that are the immediate causes of natal and neonatal deaths.

In 1939-40 there were 5300 viable births at the Maternity Pavilion of the Royal Infirmary, Edinburgh, and in this total there were 650 deaths. Of the 650 deaths, 414 were natal deaths and 256 were neonatal. The preponderance of still-births over neonatal deaths in this hospital series is heavier than it is in national figures (see Table); but it may be said that a definite preponderance is always present.

Of this total of 650 deaths, the cause of death was determined by post-mortem examination in 541 cases by Dr Agnes Macgregor. The main pathological groups were major congenital defects (for example, spina bifida, anencephaly, alimentary atresias, heart defects), asphyxia, intracranial hæmorrhage, various kinds of infection, a group of miscellaneous conditions, and a group where no cause of death was found Congenital defects can be briefly dismissed; they formed a small but appreciable number of the total, and represent an inevitable and not regrettable loss. But asphyxia and intracranial hæmorrhage together accounted for a very large number of cases. Fatal congenital defects, asphyxia and intracranial hæmorrhage are problems that belong to the obstetrician; they are created by conditions in the mother in pregnancy and labour. These three pathological conditions account for nearly all the still-births, and in this series for about three-quarters of the neonatal deaths. This brings out two important facts—the close link between natal and neonatal deaths, and the allocation of the majority of neonatal deaths as an obstetrical and maternal problem.

Neonatal Infection.—There remains the problem of infections. In this series they formed a negligible part of natal deaths—less than 1 per cent But they accounted for 27 per cent. of the neonatal deaths. Neonatal infection is thus a substantial factor in neonatal deaths, and some general remarks must be made about it.

In the uterus the fœtus is completely protected from surface bacterial invasion But with the rupture of the membranes, and during the movement of the face and body through the vagina, the eyes and skin become exposed to bacterial attack, while infection of the throat, lungs and stomach may also take place during birth through swallowing and breathing. After birth, the baby is open to attack from several fronts, the whole

But still-births (natal deaths) must be added to neonatal deaths, if we are to appreciate the full aggregate of infant deaths in the first month and compare it with the loss for the remaining eleven months. This comparison is shown in still-birth, neonatal, and infant mortality rates in Scotland and Holland for the year 1938. (The Scottish still-birth rate is for 1939)

TABLE

	Natal Death-rate (Still-births)	Neonatal Death rate	Natal and Neonatal Death-rate	Death-rate One to Eleven Months
Scotland	42	35	77	35
Holland . .	25	21	46	15

These figures show the total mass of natal-neonatal deaths, and also that in countries like Holland, which have succeeded in bringing infant mortality rates to a low level, the loss of life during birth and in the first month remains the hard and stubborn core of the problem of infant mortality.

Causes of Natal-Neonatal Deaths. — *All these deaths are* now registered, and the certificate bears also the cause of death, which is determined in the great majority of cases by clinical examination. This clinical certification specifies such conditions as prematurity, congenital debility, asphyxia, atelectasis, intra-cranial hæmorrhage, and a smaller number of miscellaneous conditions. But the clinical diagnosis of neonatal diseases is difficult and uncertain, and their clinical certification is often inaccurate and unreliable. Therefore many certificates in these cases of doubt resort to such terms as prematurity and congenital debility which are only predisposing conditions and which throw no light on the actual causes of death. The clinical certification of natal and neonatal deaths gives little help, and is often positively misleading in determining the underlying pathological problems. It is only by post-mortem examination of a large number of these cases that the immediate cause of death can be ascertained.

There are on record many hospital autopsy series of natal and neonatal deaths—for example, those of Spencer, Eardley Holland, Cruickshank and F. J. Browne. These are hospital cases, and they form probably an untrue sample of births throughout the population; and again, one hospital differs from another in the proportion of normal and abnormal births. With these reserva-

of prematurity, not on a basis of time of gestation, but on a standard of weight at birth. This recommendation has been generally adopted in maternity hospitals in Europe, America and Australasia. The new standard is of a birth-weight of 5½ lb. or less (2500 grammes). This weight-standard has been of great value in securing a more accurate study of the incidence and mortality of prematurity; but it still leaves room for fallacies, in not fixing a lower weight standard for non-viable prematures and in not including premature still-births The upper-weight standard has been well chosen, because premature babies above that weight meet the risks of birth and of the neonatal period almost as well as full-time babies; while these risks rapidly increase under 5½ lb. But it must be emphasised that a complete study of prematurity must include premature still-births, as well as prematures that survive birth.

With this new standard let us examine the problem of prematurity, in order to know its extent and its contribution to mortality during and after birth. In the Edinburgh series of 5300 viable births already mentioned there were 653 premature and 4647 mature infants on the Genevan standard of weight. The total of deaths (still-birth and neonatal) was 650; of this total, premature babies accounted for 349 (that is more than half) and mature babies, 301. Of the premature deaths, 210 were still-births, and 139 neonatal deaths. These figures are not easy to grasp, but the facts which they show may be stated simply. In a large maternity hospital the incidence of prematurity on this new weight standard was 12 per cent. This small proportion of all the babies contributed half (and a little more) of the total deaths during birth and a short stay in hospital. The total death-rate in this group of viable prematures was 53 per cent., this rate including still-births and neonatal deaths. The neonatal death-rate in prematures that survived birth was 31 per cent. The significance of these facts and figures is shown in Fig. 1, where the blocks of deaths, mature and premature, natal and neonatal, are shown in an accurate spatial relationship to the total surface occupied by 5300 viable births

It is clear that the problem of prematurity is of major importance in the whole problem of still-births and neonatal deaths. But prematurity is not of itself a cause of death; it is an immature condition of body in which death is more likely to occur either during birth or soon afterwards. The great lethal factors remain the same as in mature babies, namely, major congenital defects,

skin surface, and the inner surfaces of the alimentary and respiratory tracts; and a surface infection can easily pass into the blood and become a septicæmia. The natural immunity of the newborn baby is low; for example, staphylococcal infection of the skin may spread rapidly in a way unusual in older children; and bacillus coli infection of the meninges and lungs, *rare after the first month of life, are not uncommon at this time.* This bacterial vulnerability of the newborn has been appreciated as regards infection of the eye and the umbilical wound, and effective measures are now taken to protect these vulnerable points. But there are other sites and forms of infection which are not sufficiently recognised, and are ineffectively dealt with. *Deep infections*, such as pneumonia, meningitis and septicæmia, seldom show distinctive clinical features, and are often only discovered by post-mortem examination; and the bacterial causes of these infections show a remarkable frequency of staphylococci and *B. coli*. *Thrush*, if confined to the mouth, is a benign infection, but when it invades and ulcerates the œsophagus, is dangerous and often fatal. The mysterious alimentary infection called *gastro-enteritis*, which is a common cause of death in older infants, also attacks the newborn. In recent years there have been numerous papers in Britain, America and elsewhere describing outbreaks of gastro-enteritis or "epidemic diarrhœa of the newborn" in maternity hospitals and nursing-homes, and with a high mortality.

Newborn babies are vulnerable to infection, and their congregation in nurseries must and does favour the spread of infection. The danger and the existence of cross-infection in children's hospitals and fever hospitals are well known; but the prevalence of fatal cross-infection in nurseries of the newborn *is not sufficiently recognised. With the trend of practice* towards more institutional midwifery, it is important that the dangers of infection of newborn babies should be realised, and should be countered by a stricter nursing technique. During 1939-1940 there were 256 neonatal deaths at the Maternity Pavilion, Royal Infirmary, Edinburgh, and of this total, about one-quarter were attributed to neonatal infection; the most frequent cause of death was gastro-enteritis, the next was pneumonia; and there were four cases of œsophageal thrush, all in premature infants

Prematurity.—A few years ago an international medical committee of the League of Nations recommended a new definition

Further, it is obvious that the dangers that threaten the premature baby in birth and during the first month do not cease then, but continue, although with less intensity, in later infancy. The problem of prematurity is therefore important and formidable

Neonatal Dietetics. Before birth the nutrition of the fœtus is by a process of direct transmission of nutritive elements from the maternal to the fœtal circulation. After birth the process is indirect by means of the special food milk and by its digestion in the alimentary tract of the baby. Neonatal feeding is the first trial of a new process, and is the first chapter of human dietetics The food and its administration constitute this new process of feeding, and there are two methods, breast-feeding and bottle-feeding. Whichever it is, the process is new and complicated, and is subject to many disturbances and difficulties. On the whole the management of infant feeding in this opening phase is poor, and the poor standard of practice is due to three main causes—our lack of knowledge of the intricate processes at work, the inadequate teaching of medical students and nurses in the subject, and the break in the supervision of the baby between the departure of the midwife and obstetrician and the arrival of the health visitor and the family or clinic doctor.

Of the two methods of feeding, breast-feeding is in theory the best, the safest, the simplest and the cheapest. But the initiation of breast-feeding is beset by many difficulties, and in practice it fails to the extent that by the third month of life 30 to 50 per cent. of babies in Britain have been weaned and are bottle-fed. Whether these innumerable early failures of breast-feeding are due mainly to failure of maternal production of milk, or to faulty management of early difficulties on the part of those who advise the mother is a subject of controversy. But it is certain that the subject of breast-feeding is neglected both in study and teaching, and that its practice could be much improved by more study of the subject. Breast-feeding is not a simple process, but a complex of three processes—lactation, suckling and digestion; and in each of the three component processes there are underlying data of structure and function which must be understood before the initiation of breast-feeding can be brought under successful management.

Bottle-feeding by cows' milk—fresh, condensed or dried—has been much improved in the last twenty years, and the benefits of this improvement have been widely disseminated by child welfare clinics and by family doctors in the same period. There is no satisfactory evidence that the nutrition of successfully bottle-fed

asphyxia, hæmorrhage and neonatal infection; but these factors operate with multiplied power.

A better control of prematurity may be attained in two ways. The first is to reduce the number of premature births by raising the standard of maternal health in pregnancy and at all times;

5300 viable births: deaths in black.

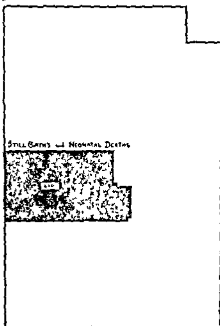


FIG 1a.

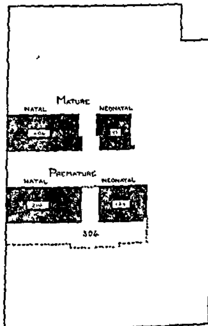


FIG. 1b.

Fig 1a shows a single black block of 650 natal and neonatal deaths in exact scale to the white enclosing surface. The total surface, black and white, contains 5300 small squares, each representing one viable birth. *In Fig 1b the single* black block has been divided vertically by the line of birth, and horizontally by a line of weight (5½ lb); *thus giving four* squares in scale, the upper two being mature still-births and neonatal deaths, and the lower two premature still-births and neonatal deaths The number of surviving premature is also *shown.*

and this is, of course, the radical solution and probably the easier to achieve. The second is to reduce the death-rate in premature babies after birth by improved methods of nursing and feeding.

These hospital figures show for premature births (on the upper weight standard of 5½ lb., and a lower weight standard of 2 lb. and including still-births) a percentage of 12 in all viable births. *It is likely that this figure* is too high for the general population, but a provisional *rough estimate of the incidence* of prematurity in Scotland may be given as about 10 per cent.

calls for a deeper study of its major problems. There are signs on many sides that the importance of the first month of life is being recognised, that its difficult problems must be attacked by combined and well-planned investigations, and that medical students, midwives and health visitors must receive more practical training in its special problems. The lowering of the natal-neonatal death-rate has been slow in every country, because its underlying problems are difficult. But those countries, such as Holland and New Zealand, that have brought down their natal and neonatal death-rates to a low level, have at the same time reduced their infant death-rates to record low levels, and in these countries the maternal and general death-rates are also low.

The first month is therefore a link in the chain of maternal and child health, and is linked also with the health of all people, young and old. Indeed, this chain of health is a circle, and the first month of life is a sensitive and strategic link in the full circle of life and health. In this narrow compass of time there is a concentration of great problems; and a deeper understanding and a better management of these problems will have a far-reaching influence in the immediate present and also in the distant future. For the movement of life is not in a closed circle, but in cycles of successive generations. As the essential links of maternal and child health are gradually strengthened, the level of health is raised throughout the whole span of life in one generation and this gain is carried into the next.

babies is inferior to that of breast-fed babies. But bottle-feeding remains the second and inferior choice of infant dietetics, because *the food itself is inferior to human milk*, and because the giving of the food is more complicated and is attended by a much higher risk of infection.

The first month of life is a critical time for infant dietetics. If feeding and digestion are successfully established by the end of the first month, it is likely that good digestion and good nutrition will continue to the end of the sixth month when the diet of milk is supplemented by other kinds of food.

Review.—Some problems of the first month of life have been considered The great mass of natal and neonatal deaths has been taken together and shown to be twice or thrice that of the deaths during the remainder of the first year. This early and massive loss of infant life has been allocated to certain pathological conditions that are the immediate cause of death—congenital defects, asphyxia, intracranial hæmorrhage, miscellaneous conditions, and infection after birth. All these problems except the last are concerned with the mother, and depend on her health in pregnancy, and the circumstances and conditions of parturition; and they belong to the obstetrician and the midwife. When labour is over, new problems appear—neonatal infection, neonatal dietetics and other miscellaneous conditions, and these to a great extent centre round the care of the newborn baby. The care of the baby in the first weeks after birth is the responsibility first of the midwife and next of the health-visitor, while the medical charge of the baby is beginning to pass from the obstetrician to the pædiatrician. The first month of life is a small part of the medical field; but in its small compass are crowded many important problems; and its problems are shared by obstetricians, pædiatricians and family doctors, by midwives and health visitors. For their solution these problems require co-operation, both in study and practice, between all concerned. Further, so far as the problems are pathological, they cannot be solved without the assistance of the pathologist and the bacteriologist, while the physiologist is needed for the study of the fundamental new mechanisms and processes that come into play after birth.

The Cycle of Life.—This first month is a small but important link in a chain which goes back through labour into pregnancy and the general health of the mother, and which also goes forward into the future life and health of the infant. The high death-rate at this time shows how easily this link can be broken, and it surely

a subject of special study. Some of the results of this study, so far as concerns the pathological side of it, are the subject of this lecture. The work has been going on, in a fairly intensive form, since 1935, but I propose to present figures for the years 1939-41 only, as these provide material sufficient for the purpose. These figures include both deaths of live-born infants within four weeks of birth (neonatal deaths) and deaths before delivery (fœtal deaths), because no study of neonatal deaths can be complete if the still-births be omitted.

During the period under review there were, in the Simpson Memorial Pavilion, 7523 live births, with 342 neonatal deaths, and 603 still-births, making in all 945 deaths. Of these, 338 live-born and 422 dead-born children were examined post-mortem, making 760 autopsies Analysis of these shows that the common causes of death fall under four headings, each embracing a large number of cases; while other causes, of which there is a considerable variety, fall into a miscellaneous group. Table I shows the incidence of each of the four principal causes of death. It must be understood that, not infrequently, these conditions are combined, and it is not always possible to know which, if any singly, has been the actual cause of death. Thus, in the frequent combination of asphyxia and intracranial hæmorrhage, it cannot always be known which has been the more important in causing death, and any decision between them must be a matter of opinion The table therefore shows, not the frequency of these conditions as actual cause of death, but the frequency of their occurrence in this series of cases.

TABLE I

Condition	Neonatal Deaths	Fœtal Deaths	Total	Per Cent
Developmental malformations	54	88	142	18.7
Intracranial hæmorrhage	135	142	277	36.4
Asphyxia	91	215	306	40.3
Infections	137	19	156	20.5
Miscellaneous	36	29	65	8.5
Inconclusive autopsy	12	63	75	9.9

The miscellaneous group included, among other conditions, hæmorrhage other than intracranial, for example, in the supra-renals, from duodenal ulcers, the stomach, œsophagus and lungs; volvulus neonatorum; venous thrombosis, most often

THE CAUSES OF FŒTAL AND NEONATAL DEATH

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IN a recent Honyman Gillespie lecture Professor McNeil spoke of the neonatal death-rate and emphasised how grave a problem it is because of the loss of young life it represents, and how intractable and stubborn, as is shown by its failure to respond in equal degree to those influences that have brought about a reduction of the general death-rate and of infant mortality. He spoke of this as very particularly a matter of concern to Scotland, where the continuing high infant mortality rate is rightly regarded as a national reproach. He suggested that the failure to produce much improvement in the neonatal death-rate is in part due to insufficient study of its causes, with consequent lack of knowledge of how to control it, so that the care and management of newly born babies may often be less than entirely satisfactory. As a means of improving the clinical care of newly born infants, and of extending knowledge of how to do this, he advocated that every maternity hospital should have an adequate, skilled pædiatric staff. To that I would add that every maternity hospital should also have a pathologist, and that he should be one who is interested and experienced in neonatal pathology. For there is no field of medicine in which co-operation between clinician and pathologist is more necessary than in this. It is recognised by all with experience of the problem that accuracy in the clinical diagnosis of neonatal disorders is often extremely difficult, and certainty in determining the cause of death is often, in the absence of an autopsy, impossible. The correlation of clinical observation with post-mortem findings may do much to help the clinical worker to greater accuracy and confidence in diagnosis ; and if we want to know the facts about the causes of neonatal death we must go, not to the registrar's certificates of death, which are valueless for this purpose, but to the post-mortem records of an experienced pathologist.

In Edinburgh for some years the pædiatric staff of the Simpson Memorial Maternity Pavilion have made this problem

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born alive, are close to or below the recognised limit of viability. It may therefore be suggested that, when a clearly viable infant dies, some cause of death other than prematurity ought to be sought. The matter may be of some importance, because if we attribute the death of a premature child to prematurity, it may be thought of, perhaps a little complacently, as something inevitable, determined when the child was prematurely born. But if we allow that a viable infant ought to live and that, when it dies, it is because some pathological condition has developed, it must be asked, why did this happen—through some accident at birth, through something done or not done after birth, through something, in short, that might have been avoided? Perhaps we shall better cultivate the preventive mind if we do not too readily ascribe the deaths of premature, but viable, infants to prematurity.

Another condition that figures frequently among stated causes of neonatal death, but is omitted from my figures, is atelectasis: the failure of the lungs to expand sufficiently to establish a satisfactory respiratory function. The reason for the omission of this very common condition from among the causes of death is that atelectasis is never more than half a diagnosis. It is not a thing that happens without cause, and when it is found in an infant that has died, it does not itself explain the death: that must be sought in some other condition, which is the cause of the atelectasis. Further reference is made to this later

Developmental malformations were found in 54 cases of neonatal death and 88 cases of fœtal death, of which 18 infants and 65 fœtuses were premature This group may be regarded as representing the irreducible minimum of fœtal and neonatal deaths. It includes such certainly or probably lethal conditions as anencephaly, spina bifida (usually accompanied by congenital hydrocephalus), cardiac defects, atresias of the alimentary tract, renal hypoplasia and aplasia, etc These, being conditions that are beyond our present power to prevent, and mostly beyond our present power effectively to treat, and representing, as they do, goods damaged in the making the loss of which is not to be greatly regretted, need not detain us further

Intracranial hæmorrhage occurred with great frequency as one of the principal causes of both fœtal and neonatal death It was found in 135 cases of neonatal death and 142 cases of fœtal death, of which 93 infants and 50 fœtuses were premature. It is met with in three common forms subdural, subarachnoid

renal; neoplasms; and erythroblastosis fœtalis and neonatorum, a disease that is only now being recognised to be much less rare than was formerly thought, and has been in our experience a much commoner cause than syphilis of fœtal and neonatal deaths, especially when these occur repeatedly in a family. Time will not allow of detailed reference to any of these conditions, and only the four principal causes of death will be fully dealt with.

Before proceeding with the further discussion of these four groups of cases it is necessary to draw attention to the enormous importance of prematurity as a factor in neonatal mortality. This is clearly shown in Table II, which presents figures derived from the cases under review.

TABLE II

	Live Births.	Neonatal Deaths	Deaths per 1000
Full-time infants . .	6815	130	19·0
Premature infants . .	708	212	299·0
All infants . .	7523	342	45·5

Put in another way, these figures show that 9·4 per cent. of all live births were premature, and that these 9·4 per cent. accounted for 62 per cent. of the deaths, while the 90·6 per cent. that were full-time births accounted for 38 per cent. of the deaths. These are striking figures and show to how large an extent the problem of reducing neonatal mortality is bound up with the prevention of premature births, or, in default of that, with the problem of the best possible management of premature infants.

I have referred to prematurity as a factor that profoundly affects neonatal mortality, not as a cause of death, because that is, I consider, how it should be regarded. This refers, of course, to degrees of prematurity within the limit of viability. This may be thought to be a wrong idea. Very many neonatal deaths, and some in older infants, are officially ascribed to prematurity. Registrars incline to give it precedence over other conditions that may be entered with it in death certificates. Yet in fact it is not often that an autopsy reveals no cause of death other than prematurity, except in cases so extreme that the babies, though

intracranial hæmorrhage is thrombosis of the dural blood sinuses, meningeal veins on the brain surface, or choroidal and other central veins in its interior. This gives rise to severe hæmorrhage, subarachnoid or intracerebral according to the site of the thrombosis. I have, however, seen this more often in rather older infants, usually suffering from malnutrition, than in the newly born, and it is not of great importance as a cause of fœtal or neonatal death.

Asphyxia.—Taking fœtal and neonatal deaths together, asphyxia ranked as the most frequent of the common causes of death. It was found in 91 cases of neonatal death and 215 cases of fœtal death, of which 70 infants and 87 fœtuses were premature. It is much the most usual important post-mortem finding in the dead-born, and is frequently found, either alone or associated with some other condition, in cases of neonatal death, especially in the premature. The cause of asphyxia is intrauterine or intranatal, and as a cause of neonatal death it operates early, though infants asphyxiated at birth may survive for a few days and then die of asphyxia. Among both still-born and live-born groups, antepartum hæmorrhage takes precedence as a cause of fœtal asphyxia, but asphyxia was found in many other cases and due to many other conditions: malpositions, obstructed and delayed labour from any cause, torsion or prolapse of the cord, and sometimes without obvious reason.

At autopsy, evidence of fœtal asphyxia is characteristic and easily recognised: profound lividity of the skin; a dusky cyanotic hue of all tissues and organs; extreme engorgement of veins everywhere; dark fluid blood; and petechial hæmorrhages under the serous membranes, especially in the thorax, and sometimes elsewhere, notably in the thymus gland. This may be all that is found, but other results are not uncommon. Among these the most important are severe and possibly fatal hæmorrhage in various situations, and certain effects on the lungs and respiratory function.

Reference has already been made to asphyxia as probably the usual cause of the intraventricular and subarachnoid forms of intracranial hæmorrhage. Other situations in which it may be concerned in producing disastrous hæmorrhage are the suprarenal glands and the surface of the liver. In the former situation it may destroy one or both suprarenals, with immediately fatal result. In the latter site blood accumulates under the capsule of the liver, where a very large hæmatoma may be formed, and

and intraventricular. All are forms of venous hæmorrhage, but they differ in cause and in the type of subject affected.

Subdural hæmorrhage is directly traumatic and is most liable to happen in instrumental deliveries, or where there is disproportion or other cause of obstruction to the passage of the fœtal head, with consequent excessive moulding and undue strain upon the folds of the dura mater (tentorium cerebelli and falx cerebri), which are liable to be torn, causing hæmorrhage from veins that course in them. It is therefore rather more common in full-time births, when the chance of obstructed labour is greater, but it is not an uncommon finding in the premature.

Subarachnoid and intraventricular hæmorrhage are much more frequent in the premature than in the mature. In particular, intraventricular hæmorrhage is hardly ever seen in a full-time infant. The cause of these types of hæmorrhage is not quite so clear as that of subdural hæmorrhage. It is probably not often direct trauma. The very frequent association of severe asphyxia with these types of hæmorrhage suggests that this is probably the principal factor. The source of bleeding in intraventricular hæmorrhage is most often one or more of the subependymal veins that run in the walls of the ventricles, especially the lateral ventricles; sometimes the choroid plexus; in subarachnoid hæmorrhage it is the veins of the pia-mater on the surface of the brain. The intense venous engorgement that accompanies asphyxia causes rupture of these veins. In asphyxiated babies it is very usual to find small subependymal hæmorrhages in the walls of the ventricles. When these burst through the ependyma, free hæmorrhage into the ventricles may result, and the whole ventricular system may be filled with blood which, on clotting, forms a cast of the cavity. Presumably the greater fragility of the veins of the premature, and the greater liability of the premature to suffer from late effects of asphyxia, account for the much higher incidence of these forms of hæmorrhage among the premature than among the mature, especially in the case of live-born infants. It has been suggested that there may be a connection between intraventricular hæmorrhage and pregnancy toxæmia in the mother. It is probable that, if this be so, it is only because toxæmia is one of the chief causes of premature births.

Extradural hæmorrhage has been rarely seen in this series. It resulted from severe injury to the skull, usually with fracture of one of the bones of the vault. An occasional cause of severe

the walls of the air-spaces as a membrane, which may form a complete lining and a most effective obstacle to the passage of air. This so-called "vernix membrane" often causes the most extreme degree of atelectasis, and usually associated with this are areas of acute emphysema, which is often interstitial as well as vesicular. The rupture of a subpleural air bulla is an occasional cause of spontaneous pneumothorax in the newly born.

In yet other cases, even without inhalation of liquor amnii or meconium, prolonged severe asphyxiation of the fœtus during birth depresses the respiratory centre so much that, although the child begins to breathe, the breathing is so feeble and shallow that very little of the lung tissue becomes expanded and is used for oxygenation. It is not unusual to find, even in an infant that has lived for some hours or a day or two, that the lungs appear, on macroscopical examination, to be totally unaerated, and sink like fœtal lungs when placed in water. It may be found on microscopical examination that air has failed to penetrate beyond the bronchioles or alveolar ducts.

In all such cases, whether with or without inhalation of foreign material, when an infant lives for hours or days without adequately expanding its lungs and respiration continues feeble and shallow, the lungs are prone to be affected with increasing congestion and œdema. This further impedes ventilation and may produce secondary collapse of aerated alveoli, gravely aggravating the condition. And lastly, in all such lungs pneumonia is apt to develop, whether from infection received during birth or after it This is especially the case when meconium or amniotic fluid has been inhaled, but it applies also to the congested and œdematous lungs of pure asphyxial atelectasis without inhalation. It has been found that nearly all cases of pneumonia in infants who die in the first three or four days are of this type, associated with inhalation of meconium, or liquor amnii, or material from the maternal passages, or with persistent atelectasis: that is to say, they are examples of what may be properly termed "post-asphyxial pneumonia"

We are now in a better position to consider the true significance of atelectasis. As has been said, it is never a complete diagnosis and should not be invoked as a cause of death Except in occasional cases when expansion of the lungs is prevented by pressure upon them by, for example, a pleural effusion, a diaphragmatic hernia or a tumour, or by a malformation of the lungs, congenital atelectasis, so-called, is nearly always the result

if this should rupture, massive intraperitoneal hæmorrhage results Hæmorrhage in both these sites in the new-born is sometimes attributed to trauma, and this may occasionally be the cause; but it is seen so often when there is no other reason to suspect trauma and ample other evidence of asphyxia that it is allowable to regard it as being usually caused by asphyxia. Another site in which asphyxia may be responsible for massive hæmorrhage is the lungs, where it may produce total consolidation of a large proportion of the lung tissue and rapidly prove fatal. It has been suggested that this massive pulmonary hæmorrhage is a form of pneumonia and due to infection, but there is little evidence to support this, and in most cases all the facts point to asphyxia as the cause.

The effects of asphyxia in the lungs, other than hæmorrhage, are less striking but more important, because more common. They are, firstly, the results of premature stimulation of the respiratory centre, before the fœtus is free of the maternal passages; and secondly, the result of depression of the respiratory centre by prolonged asphyxia, so that respiration fails to be satisfactorily established after birth. Both in live-born infants and in dead-born fœtuses that have been severely asphyxiated during birth, evidence is commonly found to show that the fœtus, in making premature respiratory efforts, has inhaled into the lungs quantities of amniotic fluid. This is readily recognised under the microscope in sections of the lungs by the presence of solid material in the fluid, especially cornified cells, lanugo hairs, and vernix from the skin of the fœtus. The lungs in such cases are water-logged, bulky and heavy, giving somewhat the appearance of pneumonic consolidation; and the condition seriously reduces the available respiratory area, and may itself be the cause of failure to establish respiration, or of a persistent atelectasis after the child has begun to breathe. The condition is aggravated if the asphyxiated fœtus passes meconium into the liquor amnii and then inhales it, when the lungs and respiratory passages may be filled, even distended with meconium, and all the bronchi blocked with it so that breathing is rendered impossible.

A remarkable effect is produced when the inhaled liquor amnii contains any large amount of vernix. This may be recognised in microscopical sections of the lungs as masses of structureless, acidophilic material lying in the bronchi or alveoli. When air enters, this material is spread out and plastered upon

mother who is suffering from a similar infection at the time. One case of fœtal meningitis is included in this series.

As a cause of neonatal death, infection is immensely important. It is common. It is far and away the most common cause of deaths of infants who have survived the immediate risks of birth and lived for upwards of three or four days. It is, of all the main causes of neonatal death, the most likely to be amenable to preventive measures. It is the one that most intimately concerns the pædiatrician, the family doctor who attends mother and child after the confinement, the nurse, the mother, and all who have to do with the care of the infant during this most critical first month of life. I shall not deal in any detail with neonatal infections, but in view of the frequency of infections in my series of cases, and of the outstanding importance of the subject, some observations must be made.

Infection afflicts the new-born in multifarious forms. Of lethal infections much the most frequent are pneumonia and gastro-enteritis As has been said, when a child dies with pneumonia in the first three or four days of life, the pneumonia is almost always of "post-asphyxial" type, and has only aggravated a condition that might well have been fatal of itself. After this time begin to appear the true post-natal infections of the respiratory tract. Frequently these take the form of a broncho-pneumonia, often confluent, essentially similar to broncho-pneumonia in older infants. Attention must, however, be drawn to the relatively high incidence of septic inhalation broncho-pneumonia in the newly born, when inhalation of regurgitated stomach contents is responsible for a destructive inflammation of the lungs. It is particularly a risk to be remembered in the case of vomiting babies.

Acute gastro-enteritis tends to occur in epidemic form, in outbreaks in the nurseries. Attempts to discover a specific infecting organism have proved abortive in almost all cases, and this complicates the problem of tracing sources of infection. The ease with which it spreads from baby to baby, and its very serious effects, make this disease a most grave problem in maternity hospital nurseries. The post-mortem findings in fatal cases vary considerably. It is not unusual to find no pathological changes of a degree in any way commensurate with the severity of the clinical effects Some inflammatory reddening of the gastro-intestinal mucosa, often most noticeable in the upper jejunum, without ulceration or even much œdema, is usually the only

of birth asphyxia, either directly by depression of the respiratory centre or indirectly through the medium of inhaled liquor amnii or meconium or vernix membrane, which are inhaled because the fœtus is asphyxiated, and occupy air space in the lungs and obstruct the passage of air. The great majority of the deaths that are attributed to atelectasis ought therefore properly to be attributed to asphyxia.

It should be added that all these late or delayed effects of asphyxia affect much more severely the premature babies. This accounts for the greater frequency of asphyxia as the cause of death in the live-born premature. The mature infant has a greater power of recuperation from the effects of asphyxia, and has a much better chance of survival if it is born alive. This may be explained by the feebler condition of the premature infant, and it is possible that the immaturity of the lungs themselves may be a factor militating against the premature infant's chance of survival.

Asphyxia has been dealt with at some length, because there is some reason to think that it is not generally understood how important asphyxia is as a cause of deaths of infants that are born alive. As a cause of fœtal death it is recognised, but many people appear to be too ready to believe that, if an asphyxiated infant can be induced to breathe, all is well and it can no longer die of asphyxia. That this is far from true is proved by the pathological findings in many cases, as described above.

Infections.—In the neonatal group, conditions coming under the heading of infections were actually of more frequent occurrence than any other of the main causes of death. As a cause of fœtal death they played a minor part. They were found in 137 cases of neonatal death and 19 cases of fœtal death, of which 75 infants and 3 fœtuses were premature. Amongst the still-births most of the infections were prenatal pneumonia. A few were congenital syphilis. It may be said in passing that syphilis did not figure at all prominently in the series of cases under consideration. There is reason to fear an increase under present conditions, but during the period under review it was not prevalent. Prenatal pneumonia is practically always of the type associated with asphyxia, with inhalation of liquor amnii, with or without meconium, or other material from the maternal passages, as already described. Cases of prenatal pneumonia when the mother had pneumonia at the time of delivery have been described but are very rare. Fœtal septicæmia occurs occasionally, infection being from the

is regarded as commensal in the bowel. This may explain the persistent failure to discover an infecting agent. But it is possible that an organism as yet unrecognised, perhaps a virus, may be the cause.

As an example of an apparently trivial infection that tends to develop dangerous characters in the new-born, no better could be given than thrush. This, usually regarded as a benign and fairly harmless oral infection, is by no means harmless to the new-born. Beginning, it may be, as a mild infection of the mouth, it may spread to the pharynx, the œsophagus, the stomach, and occasionally even to the intestine, producing widespread and sometimes deep ulceration, and attended by the most serious clinical effects and not infrequently ending in death. In such cases the baby often develops a septic inhalation broncho-pneumonia, in which the thrush organism is found along with others, in the bronchi and lungs.

It follows from all this that any manifestation of infection in a newly born baby, no matter how apparently trivial, must be taken seriously. It follows also that, in the matter of prevention, seeing that not only the recognised virulent pathogens, but also other common and less obviously dangerous organisms, are capable of producing such disastrous effects, the most stringent precautions must be taken to guard against infection. And this applies with especial cogency to nurseries in hospitals and elsewhere, where numbers of young and susceptible infants are gathered together and where, therefore, the danger of infection, occurring in epidemic form and gaining virulence in passage from child to child, is constantly present. It is therefore incumbent on all who are responsible for the welfare of the babies to realise that the price of freedom from neonatal infection is eternal vigilance.

abnormal feature, sometimes accompanied by degenerative changes in the liver.

One fact about infection in the new-born needs to be emphasised. Newly born infants are highly susceptible to infection by common organisms, even by some that are not usually regarded as highly pathogenic. This susceptibility manifests itself in a proneness to serious developments in infections of all kinds, and in the appearance of organisms of supposedly low virulence as the cause of serious, even lethal, lesions in quite unusual situations. A few examples will illustrate this.

As a first example may be cited the case of staphylococcal infections. *Staphylococcus aureus* always has the potentialities of a dangerous pathogen, but it is not familiar as the sole cause of a form of primary pneumonia. When it plays a part in a case of pneumonia in an older person it is usually as a concomitant or complicating factor in an infection that is primarily due to another cause, for example, influenza. In infancy, and especially in the neonatal period, primary staphylococcal pneumonia, without any accompanying or antecedent infection, is far from uncommon. It produces a rapidly developing suppurative inflammation beginning in the bronchi and quickly producing disorganisation of large extents of the lung tissue, with formation of multiple abscesses and rapid development of acute empyema or pyo-pneumothorax. This sometimes results from septic inhalation, but often it is a true primary infection of the respiratory tract. There may also be mentioned the risk of generalisation in the form of septicæmia or pyæmia, of apparently trivial staphylococcal skin infections.

Perhaps the best example of the peculiar susceptibility of the new-born to infection by common organisms of supposedly low virulence is the frequency and variety of lesions produced by organisms of the *B. coli* group. These are familiar as pathogens in the urinary tract, the peritoneum and other (usually abdominal) situations. As a cause of pneumonia, pleurisy, and meningitis they are not familiar, except in the neonatal period. In the first month, and especially in the first three weeks, no organism is more often the cause of pneumonia, no organism is so often the cause of meningitis. Yet after the first month they are virtually never found in either rôle.

It may be that epidemic gastro-enteritis affords another example of the pathogenic action of some common organism that

TABLE II

Relation of the Cause of Death to the Age at Death in 369 Infants

Condition	Age				
	1st Week.		2nd Week.	3rd Week.	4th Week.
	1-3 Days.	4-7 Days.			
Asphyxia	99	4	2	1	0
Infection	3	7	30	32	9
Intracranial hæmorrhage	48	5	4	0	0
Developmental malformations	24	15	10	2	0
Prematurity	37	4	4	1	0
Miscellaneous	7	10	5	3	1
	218	45			
	263		55	39	10

asphyxia, intracranial hæmorrhage, prematurity and developmental malformations. It will be noted that infections rarely cause death in the first three days and that only a few die from them in the latter part of the first week. A complete reversal of the picture occurs after the first week, the vast majority of deaths being caused by infection. Seventy-one died from infection in the 2-4-week period, and only 33 from all other causes. It will readily be appreciated that the four conditions which account for the majority of neonatal deaths in the short space of the first three days represent the hard core of neonatal mortality. No drastic reduction in their incidence can be anticipated, but care of the expectant mother, especially in the nutritional field, and a universally high standard of obstetrics will effect some improvement. Infants who survive the first few days should, with few exceptions, be on safe ground if a high standard of care is provided. This is seldom attained in institutions caring for large numbers of infants, with the result that there is much preventable acquired disease in the neonatal period. Infections are much the commonest and most dangerous of these acquired diseases, and, as I have illustrated on the chart, they are the principal cause of death in infants surviving the first week (Fig. 1). A drastic reduction in the incidence of preventable infections, notably epidemic gastro-enteritis, is the most urgent problem

INFECTION IN THE NEWBORN

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In the Simpson Maternity Pavilion, during the three-year period, 1940-42, there were 7863 live-births, and 212 infants were admitted from the hospital district and elsewhere shortly after birth. Thus, 8075 infants passed through the hospital in the period under review: 382 of these infants died in the hospital within a month of birth; but it must be borne in mind that the vast majority of infants are discharged from a maternity hospital in the second half of the second week of life, and some of these die before reaching the age of one month. The cause of death was assessed in 369 of the fatal cases by reviewing all the obstetrical, clinical and pathological evidence. No assessment for statistical purposes was made in the remaining 13 cases, owing to the absence of pathological data which provide much the most reliable indication of the cause of death in the vast majority of cases.

The incidence of the principal causes of death in this series is shown in Table I. The relation of the cause of death to the age at death is shown in Table II.

The great preponderance of deaths in the first three days of life is well illustrated in Fig. 1. More infants die in these three days than in the whole of the remainder of the first month. The causes of this high initial mortality, in order of frequency, are

TABLE I

The Incidence of the Principal Causes of Neonatal Death in 369 Infants

Condition.	No of Cases	Incidence Per Cent.
Asphyxia	106	28·8
Infection	81	22·0
Intracranial hæmorrhage	57	15·4
Developmental malformations	51	13·8
Prematurity	46	12·5
Miscellaneous	28	7·5

Read 19th August 1943

TABLE III

The Incidence of Various Neonatal Infections in a Total of 8075 Infants born in the Simpson Maternity Hospital in the Three-Year Period, 1940-42. The Death-Rate from Each Infection is also shown*

Disease.	No of Cases.	Incidence.	No. of Deaths	Mortality Per Cent
Conjunctivitis	1284†	15·9	0	0
Staphylococcal skin infection	550	6·8	0	0
Thrush	395	4·9	6	1·5
Gastro-enteritis	102	1·25	57	56
Infection of respiratory tract	42	0·5	2	5·0
Pneumonia, primary	11	0·14	11	100
Pyelitis	7	0·09	0	0
Omphalitis	6	0·07	0	0
Septicæmia	5	0·06	5	100
Meningitis	3	0·04	3	100
Congenital syphilis	?	?	2	?

* 112 infants, mostly premature, were admitted to the hospital shortly after birth

† Approximate figure based on accurate records kept for six months and including the mildest cases, but excluding silver nitrate reactions.

thrush 6 deaths with a mortality rate of 1·5 per cent There were 5 cases of septicæmia, all fatal, 3 of meningitis, and 2 infants died from the effects of an epidemic infection of the respiratory passages. It is a startling fact that the great majority of the 86 deaths from infection in the three years were preventable

I will now consider the four common infections in more detail, commencing with the two which affect the alimentary tract.

Gastro-Enteritis

Epidemics of gastro-enteritis are a nightmare to both pædiatricians and nurses. The prevalence of this grave disease in maternity hospitals in New York led to an inquiry by Rice (Commissioner of the Bureau of Preventable Diseases, Department of Health, New York City) and his associates, who published their results in 1937. These workers reported 505 cases of epidemic diarrhœa in eleven maternity hospitals in New York in the 2½-year period, June 1934 to December 1936. The case incidence was the very high one of 14 per cent. and the mortality rate 46 per cent. The earlier literature contains surprisingly few references to such a common disease, but numerous publications have appeared in the last few years.

confronting administrators and staff of all large maternity hospitals at the present time.

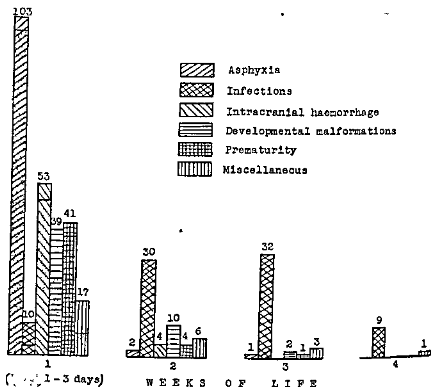


FIG. 1.—The relation of the cause of death to the age at death in 369 infants

Incidence of Various Neonatal Infections in a Maternity Hospital

The incidence of the various infections is shown in Table III. The first six conditions mentioned in the table—conjunctivitis, staphylococcal skin infections, thrush, gastro-enteritis, infection of the respiratory passages and primary pneumonia—are the common infections in that order of frequency. The other infections are uncommon and are, therefore, of minor importance. When examined from the point of view of mortality rather than frequency the relative importance of the various infections appears in its true light. Gastro-enteritis caused 57 deaths in the three years, with the high mortality rate of 56 per cent., many more than all the other infections combined Primary pneumonia caused 11 deaths with a mortality rate of 100 per cent., and

Clinical Features.—The first sign of illness seldom appears before the end of the first week; it is a sudden loss of appetite. This should always suggest the possibility of gastro-enteritis, particularly if the disease is prevalent at the time. Diminished vitality, a tired sickly appearance and pallor follow within a few hours. Diarrhœa as a rule develops within a similar time, but may be delayed for twenty-four hours or longer. The stools are watery in most cases and are usually yellow. They frequently

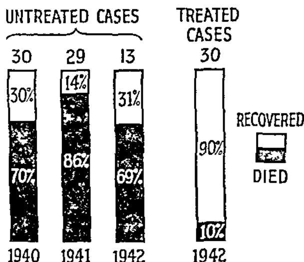


Fig. 3.—The mortality rate in gastro-enteritis before and after the introduction of sulphaguanidine therapy.

exceed ten a day. Signs of dehydration usually appear by the second day, and the weight course shows a rapid fall. Fever is an inconstant feature and vomiting is often absent. Unless appropriate treatment is commenced early, dehydration and weight loss progress rapidly, abdominal distension appears and weakness and anorexia soon become extreme

Treatment.—The introduction of sulphaguanidine has caused a dramatic fall in the mortality. Fig. 3 shows the mortality rate in the Simpson Maternity Hospital before and after the inception of sulphaguanidine therapy. I published the method and results of treatment with this drug in the *British Medical Journal* of 3rd April (Henderson, 1943). I would like to emphasise three points regarding treatment: (*a*) The importance of giving large doses of the drug—½ gm. four-hourly for mature and ¼ gm.

Ormiston (1941) published his observations on 139 cases in three maternity hospitals in England during 1940. There is much to be said for the compulsory notification of neonatal gastro-enteritis occurring in maternity hospitals, as instituted by Rice in New York after his inquiry. If a similar step were taken in this country it would reveal an alarming state of affairs, because I am convinced that few maternity hospitals are exempt from periodic epidemics of this disease.

Ætiology. — The incubation period varies from two to twenty-one days with an optimum of four days (Abramson and Frant, 1938). The causal bacterium or virus still eludes identification. Some believe that normal inhabitants of the

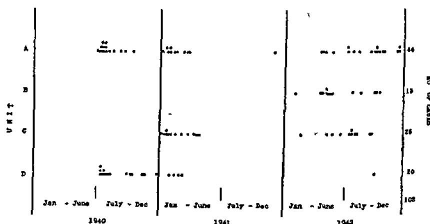


FIG. 2 —The distribution of gastro-enteritis cases in the three years 1940 42

bowel may cause the disease by assuming pathogenic properties in the newborn, in whom resistance is low, and produce epidemics by gaining in virulence through passage.

Incidence and Mortality.—There were 102 cases in the three years under review. Fig. 2 shows the distribution in each of the four hospital units. The epidemic character of the disease is clearly shown, and it will be noted that an epidemic in one unit usually spreads to one or more of the other units. The incidence was approximately 1·5 per cent It was much higher in premature infants, in whom it was 7 per cent. compared with 0·7 per cent. in mature infants. A longer stay in hospital, crowding in premature nurseries and universal bottle-feeding are probably the main causes of the higher incidence in premature infants. Fig. 3 shows the mortality in each of the three years.

disease may easily be overlooked. In *The Lancet* of 17th January last year, Dr Gilbert Ludlam and I (Ludlam and Henderson, 1942) published the results of an investigation in the Simpson Maternity Hospital. The following observations are based principally on our work.

Ætiology.—Thrush is a specific infection caused by the yeast-like fungus commonly known as *Monilia albicans*. The fungus produces the thrush lesion by infiltrating areas of the buccal mucosa with a meshwork of pseudo-mycelial strands.

Incidence.—One hundred and sixty-three cases were observed in 1940, an incidence of 6·3 per cent. The incidence fell to 4·7 per cent. in 1941 and 3·7 per cent. in 1942 owing to stricter isolation following our investigation. Fig. 5 shows the distribution of the 163 cases in the four units of the hospital during 1940.

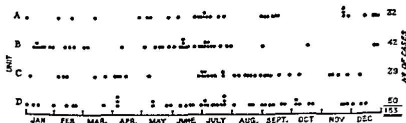


FIG. 5.—The distribution of thrush cases in the year 1940

It illustrates the endemicity of the disease and the periodic occurrence of epidemics. Sixty unselected infants were investigated by swabbing their mouths at intervals during the first ten days of life. *Monilia albicans* was isolated from 11 (18·3 per cent.); all developed thrush within a few days. It would appear, therefore, that inoculation of the mouth of newborn infants with this organism usually causes thrush. The incidence of the disease was several times greater in bottle-fed than in breast-fed babies

Clinical and Pathological Features.—Daily inspection of the mouth for thrush lesions should be a routine procedure in maternity hospitals. The lesions may vary in size from pin-head spots to large plaques. They are adherent, greyish-white in colour, and may be found on any part of the lips, tongue or buccal mucosa. They enlarge and multiply rapidly.

Oral thrush does not produce any ill-effects unless there is a heavy infection, but in severe cases the associated stomatitis may interfere with feeding. The lesions spread, not infrequently, to the pharynx, and even the œsophagus may be invaded. Severe

three-hourly for premature infants; (*b*) the importance of withholding milk completely until the appetite returns—this may not occur for several days; (*c*) the necessity of giving a high fluid

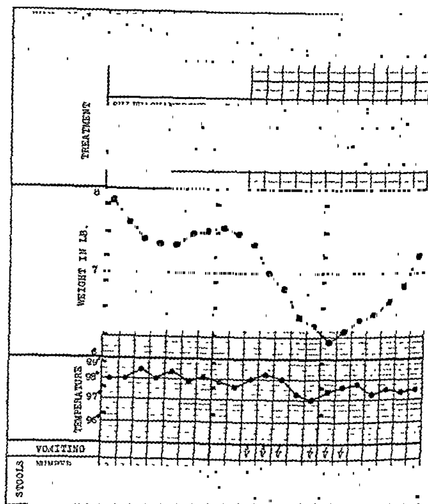


FIG. 4.—The clinical chart of Baby L (S M H., No. B3447), who developed acute epidemic gastro-enteritis on the tenth day of life, showing the course of the disease and the treatment.

intake, by gavage if necessary. The treatment of a recent case is shown on the chart in Fig. 4.

Thrush

Oral thrush is endemic in many maternity hospitals and infants' institutions. Its prevalence is often not recognised, as the

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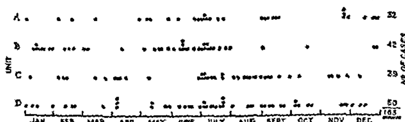


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Oral thrush does not produce any ill-effects unless there is a heavy infection, but in severe cases the associated stomatitis may interfere with feeding. The lesions spread, not infrequently, to the pharynx, and even the œsophagus may be invaded Severe

three-hourly for premature infants ; (*b*) the importance of withholding milk completely until the appetite returns—this may not occur for several days ; (*c*) the necessity of giving a high fluid

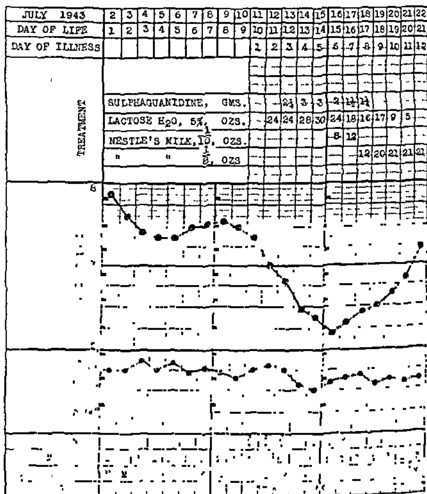


FIG. 4.—The clinical chart of Baby L. (S.M.H., No. B3447), who developed acute epidemic gastro-enteritis on the tenth day of life, showing the course of the disease and the treatment.

intake, by gavage if necessary. The treatment of a recent case is shown on the chart in Fig. 4.

Thrush

Oral thrush is endemic in many maternity hospitals and infants' institutions. Its prevalence is often not recognised, as the

lesions. In the years 1941 and 1942 I kept notes on all infants with staphylococcal infections of the skin and of all cases of maternal mastitis, and for six months during the latter part of 1942 and the beginning of 1943 I kept daily notes on all cases of conjunctivitis. I am indebted to Dr Ludlam for carrying out the bacteriological part of the investigation which was chiefly devoted to conjunctivitis.

The incidence of the various clinical types of staphylococcal infections in 1942 is given in Table IV. Staphylococcal conjunctivitis is much the commonest staphylococcal lesion. There were as many cases of staphylococcal conjunctivitis in the year under review as of staphylococcal skin lesions of all types. I will not say anything further about conjunctivitis at this juncture. There were 209 infants with staphylococcal skin lesions, an incidence of 7½ per cent. The lesions were usually small, few in number and transient, but occasionally they were more severe and persistent. Table IV shows that more than half

TABLE IV

The Incidence of the Various Types of Staphylococcal Infection (based on the type of the initial lesion) in 424 Infants in the Year 1942

Type of Lesion.	No of Cases		Incidence Per Cent
Conjunctivitis .	212*		50 0
Pustules	115	212	27·1
Paronychia	53		12 5
Bullous impetigo	26		6 1
Boils	10		2 4
Cellulitis and abscesses	5		1 2
Pneumonia	3		0 7

* Equivalent of 106 in six months of accurate recording

were pustular and that paronychia, which comes next in frequency, was much commoner than bullous impetigo. Boils and cellulitis with abscess formation were uncommon More than one type of staphylococcal lesion was found in a minority of affected infants; and skin lesions, particularly pustules of the face and eyelids, and paronychia, were associated with staphylococcal conjunctivitis in a significant number of cases. The mildest forms of staphylococcal dermatitis are almost endemic in the infant population of maternity hospitals, but the more severe

œsophagitis, which can seldom be diagnosed with certainty during life, causes complete anorexia and persistent regurgitation, followed by inhalation bronchopneumonia. In the three-year period under review 13 infants were found to have thrush œsophagitis at post-mortem and 7 had died from its effects. The infection had spread to the stomach in two cases Invasion of the blood-stream has been reported on several occasions This is not surprising as the mycelial filaments penetrate deeply and readily invade lymphatics and blood vessels. The organism usually seems to perish in the blood-stream but may produce lesions in many parts of the body.

Treatment. — The bi-daily application of a 1 per cent. aqueous solution of gentian-violet for a few days, followed by daily applications for a longer period, is now the routine method of treating oral thrush

Epidemiology.—We showed that infants harbouring *Monilia albicans* in the mouth pass it in the stools in a high proportion of cases and contaminate their hands in about 50 per cent. These facts show how the infants' clothes and the nurses' hands become contaminated. A considerable proportion of adults harbour the organism in the throat. Todd (1937) found it in 14 per cent. of 1000 adults We found it in 33 per cent. of 60 nurses in the maternity hospital; this high incidence was probably the result of infection of nurses from infants. The organism was isolated from the fingers of nurses when bottle-feeding babies in 7 per cent. of the 42 nurses swabbed—a significant proportion. The importance of vaginal infection in the mother—a common condition—was also investigated. No significant difference in the incidence of infection with moniliæ between the infants of women with vaginal mycosis and those of controls was found, but Woodruff and Hesseltine (1938) found thrush lesions in 21 per cent. of the infants of mothers with vaginal mycosis compared with 1 per cent. in controls. We found the organism in 5 out of 10 samples of unboiled breast-milk which is used chiefly for feeding premature infants. Plates of Sabouraud's medium exposed for long periods in the nurseries seemed to exclude air-borne infection as an important factor in the spread of the disease.

Staphylococcal Infections

The *Staphylococcus aureus* is the commonest cause of neonatal infection in maternity hospitals, and it causes a great variety of

nurses were nasal carriers. The carrier rate fell during the decline of the outbreak and reached 25 per cent. six months after its peak. Almost 100 per cent. of infants of ten days old in the nurseries were nasal carriers, but only 10 to 15 per cent. carried the organism in the throat ; this is in agreement with Dr Ludlam's observations in this hospital. Benians also found 30 per cent. of women admitted for labour carried *Staphylococcus aureus* in the anterior nares. The presence of the organism in the nose is not usually associated with any obvious lesion, but folliculitis occasionally develops, and Benians believes that cases of nasal folliculitis are the principal source of infection. Droplet infection from the nose is thought to be rare, even in sneezing, when almost all the droplets come through the mouth. Benians showed that the used handkerchief is the main source of aerial contamination and spread from one person to another. Cultures from the air of the wards during the epidemic did not show *Staphylococcus aureus* in large numbers, even during bedmaking, and they could rarely be grown from fomites such as door handles. Organisms were numerous on the fingers after handling contaminated handkerchiefs, but far fewer when gloves were worn Benians also showed that implantation of the infection from the vagina is rare, that the organism is present, intermittently, on the skin of the majority of newborn babies from the first day, and that there is a great preponderance of implantation on the exposed areas. The development of staphylococcal lesions in the individual infant must depend on either subnormal resistance of the infant or exalted virulence of the organism, usually produced by passage through actual lesions in an epidemic, or by a combination of both factors

Conjunctivitis

During three periods within the last year, together totalling twenty-six weeks, I made films and direct cultures from all cases of neonatal conjunctivitis in the three main units of the maternity hospital.

Chemical conjunctivitis following the routine prophylactic instillation of 1 per cent. silver nitrate is the commonest type of conjunctivitis in maternity hospitals Silver nitrate accounts for the vast majority of cases in the first two days of life and usually produces characteristic features. Specimens taken from these cases were almost always sterile. Table V shows the incidence of the various types of infective conjunctivitis in the 1140 infants

forms, particularly bullous impetigo, often show an epidemic incidence. In epidemics a tendency for a particular kind of lesion to predominate can sometimes be seen; there was an unusually high proportion of cases of paronychia in one unit in the last three months of the year. The distribution of cases of mastitis did not show any significant relationship to epidemics of staphylococcal skin infections in the infants, neither did that of staphylococcal conjunctivitis.

Clinical Features.—I cannot enter here into a detailed description of the different types of lesion. I would, however, point out that pemphigus is a fulminating type of bullous impetigo, the difference between the two conditions being merely a matter of degree. The nail-fold infections are usually multiple. There is often a lesion on each side of the nail and both hands are often affected. Infection seems to enter small tears of the skin which are probably produced when the fingers are rubbed with a towel. The initial inflammation is soon followed by a point of suppuration in the centre. This is soon replaced by a crust in most cases, but not infrequently infection of the nail-bed occurs with the loss of the nail, or vesiculation of the skin of the finger is produced.

Treatment. — This is simple and consists of immediate isolation, the application of an antiseptic such as an aqueous solution of 1 per cent. gentian-violet to the affected area, and the covering of the part with a dry dressing to prevent the inoculation of contiguous areas or spread by contacting clothes. In the case of bullous impetigo it is essential to remove every vestige of elevated skin before applying the dye to prevent further extension of the lesions. In protracted cases 1 per cent. ichthyol paste should be applied for two days after each three-day period of dye treatment to counteract the drying effect of the latter on the skin.

Epidemiology.—Benians (1943) recently published an account of a bacteriological and epidemiological study on staphylococcal infections in infants in a maternity hospital It supplies most of the unavoidable omissions in our own investigation and I propose to quote some of his results. He confirmed the observation of other workers that a high proportion of infants and people of all ages carry the *Staphylococcus aureus* in the anterior one inch of the nares, which appears to be an ideal locus for its growth. At the height of an epidemic of bullous impetigo and other staphylococcal skin lesions he found that 85 per cent. of the maternity

but these may gain access to the fœtal circulation via placental lesions as in syphilis and tuberculosis. Ultra-microscopic viruses, on the other hand, can pass through the placental membrane, and women who develop smallpox or measles, for instance, in pregnancy, may transmit the disease to the fœtus. Labour may be precipitated, particularly towards the end of pregnancy, and the infant be born with a rash or develop one within a few days. These forms of intra-uterine infection are uncommon as most women have the virus diseases during childhood. Tuberculosis is rarely acquired in this way. Syphilis remains the most common and important form of intra-uterine infection.

Intra-Partum Infection

The principal types of infection acquired during birth are gonococcal and other types of conjunctivitis, oral thrush, and pneumonia following the aspiration of infected vaginal secretions during partial asphyxiation.

Susceptibility of the Newborn Infant to Infection

The poor resistance of the newborn infant to bacterial attack is shown by the prevalence of infections produced by organisms of relatively low pathogenicity. Thrush and certain types of staphylococcal skin lesion, such as bullous impetigo and paronychia, are infrequent in older infants and rare in adults; while *B. coli* meningitis and pneumonia, which are usually septicæmic manifestations, are virtually unknown after the first month of life. These peculiarities in the type of infection found in the newborn depend largely on immunological phenomena.

Immunity in the Young Infant.—

A. Specific Immunity.

1. Passive (transplacental), declining
2. Active, developing.

B. Tissue Immunity

1. Heredity
2. Maternal nutrition in pregnancy.
3. Maternal health in pregnancy.
4. Maturity at birth
5. Maternal nutrition during lactation; or Satisfactory artificial feeding.

A. Specific Immunity.—The degree of susceptibility to various

TABLE V

The Incidence of the Various Types of Infective Conjunctivitis in Infants

Bacterium.	No. of Cases		
	Pure Culture	Mixed Culture	Total
Staphylococcus aureus	95	11	106
" *albus*	5	10	15
Diphtheroids	9	9	18
Streptococcus viridans	6	2	8
Pneumococcus	3	3	6
Gonococcus	2	0	2
Bacillus coli	6	1	7
" *proteus*	2	1	3
" *pyocyaneus*	2	1	3
" *lactis aerogenes*	1	0	1
" *Morax-Axenfeld*	1	0	1
Negative film and culture		...	63

Infants with a pure culture	132
" " mixed culture	19
" " negative culture	63
Total of infants with infective conjunctivitis	214
Incidence of infective conjunctivitis	15·9 per cent

coming within the scope of the investigation up to the time of their discharge from hospital. Although mostly infective, some of the cases of conjunctivitis giving negative results may have been caused by prophylactic chemicals.

The most striking points in the table are the overwhelming predominance of *Staphylococcus aureus* conjunctivitis over all other types and the very small number of cases of gonococcal conjunctivitis—there were only two. The large number of cases of infective conjunctivitis—214 with an incidence of 15·9 per cent.—is also noteworthy, but I must explain that every infant showing the slightest degree of conjunctivitis was included in this study.

Streptococcal Infection

Streptococcal infection is still the most troublesome form of infection in the puerperal mother, but it seldom occurs in the newborn infant owing to the antiseptic precautions taken with umbilical dressings

Antenatal Infection

The fœtus *in utero* is protected from most types of bacterial infection. The placenta is impermeable to microscopic bacteria,

abnormal pregnancies, miscarriages, premature births, still-births, and of infants showing significant illness—mostly infective—in the first few months of life was most striking. The figures of the Toronto experiment are given in Table VI. The babies in both groups received the same food and attention, yet six months after birth the babies in the supplemented group could usually be distinguished by their much healthier appearance. These clinical experiments provide a most convincing demonstration of the important influence of optimal maternal nutrition on the

TABLE VI

The Effect on Mother and Child of Supplementing the Deficiencies in a Poor Pregnancy Diet (*Ebbs* et al, *Toronto*)

	Poor Diet.	Optimum Diet.
Abnormal pregnancy	34 per cent	6 per cent
Miscarriage Premature birth Still-birth	17 4 per cent	2 2 per cent
Infant morbidity in early months (infections+)	72 per cent	19 per cent

developing fœtus and young infant. Further reference need not be made to all the other factors influencing tissue immunity, but I would like to emphasise the fact that premature infants are much more susceptible to infection than infants born at term, chiefly because of immaturity of the mucous membranes. The importance of adequate maternal nutrition during lactation also needs emphasis The breast-fed infants of poor women not infrequently suffer from rickets, particularly in winter, and they are more prone to infection, notably of the respiratory and alimentary tracts. Optimum infant nutrition can only be attained by breast-feeding from a mother on an adequate diet Artificial feeding can never be a perfect substitute The incidence of death from infection is many times higher in artificially fed than in breast-fed babies.

The Prevention of Cross-Infection in Maternity Hospitals

You will have realised from the evidence I have placed before you that this is a most urgent matter. All investigators are

organisms in the early weeks depends to a considerable extent on the degree of immunity possessed by the mother and the extent to which this is passed on to the infant. Specific immunity is therefore passive in the early weeks, but a degree of active immunity to various organisms soon develops as a result of exposure to them after birth.

The human fœtus receives its maternal antibodies via the placenta, unlike the young of the lower mammals, such as the calf and the pig, which obtain theirs from the colostrum. Dissimilarity of placental structure accounts for the different method of passively immunising the young. Euglobulin, with which the antibodies are identified, can pass through the single epithelial layer of the human placenta, but the much thicker placental membrane of the lower mammals is permeable only to crystalloids. In these animals euglobulin is secreted in large quantities in the colostrum, which is more abundant than in the human mother; and colostrum is therefore vitally important to them. Theobald Smith (1922), in a classical experiment, showed that the majority of a batch of newborn calves deprived of colostrum died within a few days of *B. coli* septicæmia, whereas the controls having colostrum remained healthy. Some antibodies such as those of measles, smallpox and diphtheria have an equal concentration in the maternal and the fœtal blood, and infants with such a good degree of passive immunity are usually protected from these diseases for at least six months. Other antibodies such as those of the various strains of *B. coli* have a much lower concentration in the fœtal than in the maternal blood, and only a slight degree of immunity is imparted; this accounts, to some extent, for the frequency of serious coliform infections in the early weeks, although poor tissue immunity in the bowel is probably a more important factor.

B. Tissue Immunity.—Local immunity also plays an important part in counteracting infection. The nutrition of expectant mothers is of great importance, the necessity for an optimum diet in pregnancy, though long appreciated, has been proved scientifically in recent years in a number of large-scale controlled experiments. Those carried out in Toronto (Ebbs and Moyle, 1942) and in London (People's League of Health, 1942) are the best known Women from a low income group, most of whom were taking a diet deficient in protein, minerals and vitamins, were given a supplementary diet to make good all the deficiencies. The great reduction in the proportion of

ventilation of wards quickly removes organisms projected into the air and maintains a low concentration of organisms therein, and that wet sweeping of the floors greatly reduces the amount of dust-borne bacterial contamination of the air. Van den Ende *et al.* (1941) showed that the heavy bacterial contamination of the air produced by bedmaking can be almost eliminated by treating the bedclothes with emulsions of refined white oils. Such precautions as I have outlined would limit cross-infection, with rare exceptions, to sporadic cases of air-borne staphylococcal infection and epidemics would be unknown. The cubicle system, often practised in nurseries as a makeshift measure, has been widely introduced in the U.S.A. with highly satisfactory results. The recommendations of Frant and Abramson (1938) following the exposure by Rice and his co-workers of the deplorable prevalence of gastro-enteritis in New York hospitals are worth perusal.

Nurses who are attending to infants should always report any personal illness before going on duty. Any infective condition such as a cold, sore throat or skin infection contra-indicates the nursing of infants, and some other duty should be allotted to the nurse if she is able for work. There is no need to wear a mask as a routine, but a mask should be worn when there is the slightest sign of respiratory catarrh if continued attention to infants is unavoidable.

I see little hope of maintaining a drastic reduction of infection by attempting to tighten up the system of nursing routine practised in the majority of maternity hospitals in this country, for the following reasons :—

1. Overcrowding of infants.
2. Inadequate nursing staff.
3. Too small a proportion of the nurses are fully trained and sufficiently experienced
4. The pupil nurses are changed to new duties every few weeks for training reasons. Therefore a considerable proportion of the nurses attending to the infants are completely inexperienced in infant care and hygiene

The cost of building, maintaining and staffing maternity hospitals safe for infants would be heavy, but the reward would be the saving of many hundreds of infant lives annually in Great Britain alone.

The prevalence of cross-infection in hospitals at the present

agreed on the fundamental causes of the high incidence of neonatal infection in maternity hospitals. These causes are—

1. Overcrowding of the infants in nurseries and the absence of barrier-nursing precautions.
2. Inadequacy of nursing staff.

After considerable experience I have come to the conclusion that the prevailing customs of concentrating large numbers of infants in small nurseries and the use of a common changing room are thoroughly bad practice, and the main cause of the prevalence of cross-infection. Is it not rational to insist that it is preferable to make cross-infection virtually impossible by adopting a policy of dispersal, rather than to attempt to carry out barrier-nursing under crowded conditions which doom it to failure? Such a policy of dispersal implies special planning and construction of maternity hospitals. Much attention has been given to the prevention of cross-infection among mothers in planning our modern maternity hospitals, but scarcely any to the more serious problem of controlling cross-infection among the infants.

I would advocate the accommodation of each mother and her baby either in a single room or in a small ward with cubicles or partitions The baby would never leave the cubicle except for weighing and would have its own toilet requisites, bath, thermometer, etc Each cubicle would have a wash-hand basin which would always be used by the doctor and nurse after attending to either the mother or the baby. Hand-washing is most important after attending to every patient, as contaminated hands are undoubtedly the principal vehicle of cross-infection among infants. There would also be a gown in each cubicle to be worn when attending to the mother or the baby. The use of rubber gloves would also be advisable, as they pick up fewer organisms than the hands (Benians, 1943), and the gloved hands are more easily washed than the bare hands and can be dipped in an antiseptic solution without injuring the skin. Moreover, they spare the nurses' hands, which often become chapped and painful with very frequent washing, especially in winter. The principal virtue of the partition or cubicle, it seems to me, is the permanent warning which it gives of the need for strict antiseptic precautions. Cubicles are no proof against air-borne infection unless the partition is complete De Waal (1938) demonstrated this at the Edinburgh Fever Hospital. He also showed that good

MATERNAL AND CHILD HEALTH

THE UNIVERSITY AND THE PUBLIC HEALTH SERVICES

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THE plans directed to the improvement of national health have placed in the forefront the welfare of mother and child. Maternal and child health presents a specially favourable field for the operation of the new policies, for it deals essentially with young life in which the environmental and other factors that make for health are relatively simple and well understood. Knowledge and science have here long outstripped practice, and the main problem is to mobilise this knowledge and science in the interests of the community. At the same time the range of life with which it is concerned is so bound up with the survival of the race at its highest levels, physical, intellectual and spiritual, that it constitutes a grave challenge to the reality and sincerity of these new policies.

The interests of the mother and child cannot be separated. Together they form a biological unit whose welfare is indissolubly linked with those influences, social, economic, nutritional, industrial, etc., that determine community health. Health is indivisible no less than peace These wider community issues must be constantly in our minds when we are formulating the policies and duties of the medical schools in the new health planning.

The Medical Schools and Community Health

At the outset it is important to appreciate the extent to which these new duties will demand a reorientation of outlook and function In a previous communication on the " Medical Schools and the Nation's Health " (Young, 1933), I have discussed this question at some length, and will here refer merely to the more general issues The first observation is that in the historical

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day, almost one hundred years after the epoch-making discoveries of Pasteur and Lister, is a poor tribute to their memory.

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ideal, infused with a conscious national purpose. Acclaimed by all parties and classes, it has become an avowed and major concern of the State. It is realised that the methods by which it is to be achieved are collective in the widest sense, involving a mobilisation of the material, the moral and the spiritual resources of the community It is a responsibility of the statesman, the economist, the teacher, the social reformer, as well as the doctor. The place of the doctor in this scheme of health has been variously defined. This is seen in the many and often vague functions which have been shaped for him in the published plans. These have varied, from the naïve picture of the doctor dispensing health like pills at so-called " health centres " to the grandiose conception of the doctor as *deus ex machina* issuing the health fiats from Whitehall. At the outset it is clear that the new duties demand a change in the education of the doctor and a change of medical front The great intellectual and material resources which in the past have been devoted to curative medicine must be able to align themselves with the yearning of the community for a life lived without deformity and disease. It is not so much an expansion of effort, though this will be great, as a rebirth that is demanded. The outlook of the schools must be oriented to health and to the environment necessary for the creation and maintenance of health Many years ago (Young, 1933), in urging the need for such leadership by the medical schools in matters relating to national fitness, I said : " We have had professors of disease. We must have professors of health . . professors of public welfare to deal with those factors in the community which are concerned with the safeguarding of the health of the worker, housing, hours of labour, industrial fatigue, etc . . We must have in the forefront of our crusade the great fact of nutrition, which should become a dominating concern of every medical school . The professor of nutrition will have within his purview the child before and after birth, the observance of boyhood and girlhood and of the adult in his various activities of relaxation, industry and old age " The schools must address themselves to such large matters of economic and social welfare and to the building up of a body of personnel—doctors, nurses, etc.—specially trained to take their place in the various collective health services, and equipped to set the standards and thus to initiate the reforms in nutrition, housing, industrial welfare, and those other manifold factors that relate to public health.

development of "public" health organised medicine has played a part of relatively small importance. The great hygienic movements of the nineteenth century—the provision of a pure water supply, the disposal of sewage, the safeguarding of the lives of factory and child workers, etc.—owed little of their origin to the medical schools or corporate medicine. These reforms were for the most part conceived and carried through by a great succession of publicists commencing with Chadwick, whilst such collective influences as general education and the increase in wealth contributed in a marked degree to the improvement in racial health. Medical discovery, such as vaccination against smallpox and the bacterial nature of infectious diseases, provided new weapons of progress, and it was furthered by the distinguished band of medical administrators who now, for the first time, began to guide the course of public health. Despite this, *it is true to* say that the vision and the creative energy behind this many-fronted line of advance have, in the main, resided in our public men and our public institutions and not in organised medicine.

The reasons for this aloofness of the medical schools at a time of such momentous developments in community health are not far to seek. These reasons must be understood clearly before we can appreciate the nature and the extent of the reforms which the schools must undergo before they can take their place in the new health movements. Firstly and chiefly, the schools by their origin and their traditions have not been equipped to exert leadership in public matters relating to health. They were built round hospitals and, in the nature of things, their outlook on teaching and research has been dominated by their concern with disease and disability. In the second place, both in his individual and his corporate capacity, the doctor, in his search for preventive measures, has constantly found himself up against factors of a social and economic nature which were beyond his control and on which he had little or no authority to pronounce. Conceiving himself powerless, he has remained impassive. Further, Medicine often found (for example, in regard to factory legislation) that it had to refrain from expressing a corporate judgment so long as the issues remained the subject of fierce political controversy. For all these reasons it has of necessity been the consciousness of the community which in the past has dictated the great reforms in matters relating to collective health.

Within recent times the concept of collective health has been lifted on to a new and higher plane. It has become a national

ideal, infused with a conscious national purpose. Acclaimed by all parties and classes, it has become an avowed and major concern of the State. It is realised that the methods by which it is to be achieved are collective in the widest sense, involving a mobilisation of the material, the moral and the spiritual resources of the community. It is a responsibility of the statesman, the economist, the teacher, the social reformer, as well as the doctor. The place of the doctor in this scheme of health has been variously defined. This is seen in the many and often vague functions which have been shaped for him in the published plans. These have varied, from the naïve picture of the doctor dispensing health like pills at so-called " health centres " to the grandiose conception of the doctor as *deus ex machina* issuing the health fiats from Whitehall. At the outset it is clear that the new duties demand a change in the education of the doctor and a change of medical front. The great intellectual and material resources which in the past have been devoted to curative medicine must be able to align themselves with the yearning of the community for a life lived without deformity and disease. It is not so much an expansion of effort, though this will be great, as a rebirth that is demanded. The outlook of the schools must be oriented to health and to the environment necessary for the creation and maintenance of health. Many years ago (Young, 1933), in urging the need for such leadership by the medical schools in matters relating to national fitness, I said: " We have had professors of disease. We must have professors of health . . . professors of public welfare to deal with those factors in the community which are concerned with the safeguarding of the health of the worker, housing, hours of labour, industrial fatigue, etc . . . We must have in the forefront of our crusade the great fact of nutrition, which should become a dominating concern of every medical school. . . . The professor of nutrition will have within his purview the child before and after birth, the observance of boyhood and girlhood and of the adult in his various activities of relaxation, industry and old age." The schools must address themselves to such large matters of economic and social welfare and to the building up of a body of personnel—doctors, nurses, etc.—specially trained to take their place in the various collective health services, and equipped to set the standards and thus to initiate the reforms in nutrition, housing, industrial welfare, and those other manifold factors that relate to public health.

Maternal and Child Health

The modern movement directed to maternity and child welfare, like its precursors in the realm of public health, sprang from community sources. On the maternity side the public concern, provoked by the persisting loss and damage each year of numerous young and healthy lives, had two results: (1) It led the State through the Local Authorities to set up clinics for the more adequate supervision of the pregnant woman; (2) it prompted the large-scale investigation of the causes of maternal morbidity and mortality especially associated with the name of Dame Janet Campbell, and it led to the appointment of a Departmental Committee, which recommended an improvement in the training of the doctor and the provision of a more adequate midwife service throughout the country (1932). Up to this time the medical schools had failed signally in such an important communal service, and it has to be admitted that even now the training of the student in some schools is inadequate because of the small size of the obstetric departments and the small number of maternity cases available for instruction. This difficulty has been partly solved in some instances by collaboration with Local Authority maternity hospitals.

The modern national movement for the protection of child health also derived its origin and its energy from public sources. It had its inception in a community conscience roused by the extent to which disability and disease were found in children when these first came under the supervision of the newly-established school medical service. The large amount of ill-health revealed in young men at the army recruiting depots at the time of the Boer War, and again during the 1914-18 War, also played an important part. Even as late as 1936, the rejection of recruits because of disease and unfitness reached 48 per cent Several more recent reports, such as that of Titmuss in *Poverty and Population* (1938), and more recently still, that in *Our Towns* (1943), convey the same lessons. There can be no doubt that the environmental conditions in which large sections of our children and adolescents have been reared were such as to deny to them the chance of developing health either of mind or of body.

The medical schools cannot escape a certain measure of responsibility for these grave reflections on our national well-being. From the beginning the schools have remained aloof from this great communal movement towards health, and there

can be no doubt that their failure has throughout deprived it of the expert medical guidance that it required and deserved. As long ago as 1933, in referring to this complacency of academic medical circles in regard to this rapidly expanding maternal and child health movement, I used words which are still strangely relevant. I pointed out that "this movement had grown to be national, and it had become an important charge on municipal health activities before it had created a ripple on the surface of organised medical opinion. . . . Despite the pressure reaching them from such different and such influential sources and the great opportunity presented to them of identifying themselves with the most important of all health movements, that directed to the young child, the medical schools even now make for the most part only a very inadequate provision for the teaching of their students in matters of infant health. . . . It is unfortunate that in regard to this beneficent social awakening to the value of child life and health the organised medical profession has lost a great chance of leadership."* Writing in 1942, Professor Charles McNeil has still found it necessary to make a similar indictment of the medical schools. He expresses a general view when he describes the present position of this country in regard to the care of the infant and child as "second-rate," and as due in the main to the imperfect training of the doctors and nurses concerned with child welfare. It is true to say that from the beginning the administration of the maternal and child welfare services of the Local Authorities has resided in the hands of those, the majority women, who by academic standards have often been very inadequately trained for their high duties. It remains to be said that the enthusiasm and devotion with which the maternity and child welfare officers have carried out their task, under a serious handicap which was not of their own making, has been beyond all praise. The writer has known large numbers of them and can speak from personal knowledge. He can also testify from his knowledge that the public service has produced a number of men and women who by their outstanding talents and personality are equipped in a special measure to take a leading position in the new academic policies directed to the improvement of maternal and child health

* It is of interest as a sign of the change in the "academic" attitude to collective health that the article from which these extracts are taken was refused when it was first submitted for publication about fifteen years ago

James Young

The University and Maternal and Child Health

We have seen that the existing arrangements for the training of the undergraduate student on these questions are inadequate. It is true that within recent years pædiatricians have been attached to some teaching maternity hospitals, and that since the 1923 recommendations of the General Medical Council some instruction is given in infant and child hygiene. But it is widely recognised that the public child welfare and school medical services, on which this instruction must be based, have not been properly organised for this purpose. In regard to the postgraduate training of doctors, consultants, nurses and health visitors the position is even worse. It may, indeed, be said that organised academic facilities for postgraduate training and for research in the hygiene of the child before and after birth are practically non-existent in this country. On previous occasions attention has been drawn to the new functions which the educational bodies must undertake in regard to these questions (Young, 1933, 1940, 1942). In the following pages these views are developed and an attempt is made to outline a policy for the establishment of schools of maternal and child health.

This planning involves two major considerations. In the first place it requires that the subject of child health should receive the highest academic recognition in all medical schools. Adequate departments must be set up, and in the universities these should be of professorial status. A lead in this direction has already been given by two universities, Edinburgh and Durham The Chair of Child Health and Life at Edinburgh, established in 1931, has under Professor McNeil's occupancy played an important part in building up an informed opinion on problems relating to infant and child hygiene. The Chair of Child Health at Durham is of recent foundation. At the moment plans are under consideration for the establishment of a university chair of child health in London to be specially devoted to research and to the postgraduate training of doctors, nurses, health visitors and welfare officers. It is clear that all such departments devoted to the study and teaching of infant and child health must be closely integrated with the maternity hospital and school. Maternal health during pregnancy and lactation and maternal training and responsibility throughout childhood are all intimately concerned with infant and child health, whilst the maternity hospital provides the clinical basis for the study of infant hygiene.

This essential unity of the mother and child in matters relating to health is expressed and emphasised by regarding the two departments as together forming an Institute for Maternal and Child Health.

The second essential in the planning of teaching and research in maternal and child health is the collaboration of the academic departments of the schools and universities with the maternity and child welfare and school medical services of the public health authorities. The importance of this consideration is apparent when we note that the public services have in the course of time assumed responsibility for the care of the health of a large majority of the mothers and children of the country. Thus, during 1941, 452,867 women in England and Wales received antenatal supervision through organised services, the bulk of which were arranged through the public welfare schemes. This figure represents 74·5 per cent of the total registered births During 1941 the health visitors made a first visit to 566,068 children under one year (97 per cent. of total registered live births) and 409,489 infants under one year attended welfare centres for the first time (69·7 per cent. of total registered live births) (*Summary Report of the Ministry of Health*, 1942).

These figures express the extent to which the health services of mother and child are under organised public control and the extent to which the teaching bodies must depend upon these public services for access to their "clinical" material It is true that the medical schools have in general established some *liaison* with the health authorities and have in a varying degree sought and obtained access to this material for the purposes of teaching and research But it is well known that, with few exceptions, this *liaison* is loose and unsatisfactory, and that neither the schools nor the public health authorities have succeeded in establishing the integration that is necessary for effective teaching and research As Professor McNeil has repeatedly pointed out, the schools have lacked the facilities for the training of their students, and, as a consequence, the public health authorities have been often compelled to staff their services with personnel inadequately trained

These considerations have an important bearing on the plans directed to the improvement in the general health services and, in particular, to those relating to mother and child. In the schemes directed to the building up of national well-being we must throughout address ourselves to the effective training of

those who will be responsible for the organisation and administration of the medical and social agencies concerned with the creation and maintenance of maternal and child health. It is clear that the shape of the structure to be set up for these purposes will depend upon the form in which the health services of the future will be crystallised. There is at the moment considerable uncertainty in regard even to the basic features of the public health organisation of the future, and this uncertainty applies to the method to be adopted for regional administration and control. In the following description the term "Local Authority" refers to the public body responsible for the maternal and child (including school) health services in the area contiguous to the medical school or university hospital.

The organisation of the new departments for teaching and research demands an approach by the medical school to the Local Authority and the drawing up of a mutually agreed plan under a committee containing representatives of both parties. In a university school the academic representatives will include the professors of obstetrics and child health and the Local Authority representatives will include the medical officer of health. In brief, the aim is to build the academic structure for teaching and research upon the maternity and child welfare services with their various activities of antenatal supervision, midwifery, infant and child supervision, health visitors, nutrition, social services, etc In this way the clinical material of the area is made available for the medical school and so co-ordinated that each year a large number of women come under supervision throughout pregnancy and confinement, and a corresponding number of infants will remain under the same unitary care throughout lactation and up to and including school age. It is clear that by this arrangement the professors of obstetrics and child health are made responsible under the medical officer of health for the clinical care and control of the mothers and children of the area. They become, in fact, medical officers for maternity and child welfare under the local health authority. This at once identifies them with those wide social activities of the health authority that are related to mother and child, such as mothercraft, nutrition, health education, etc., and thus opens out a new era in the history of the schools. It at once establishes the professor as a professor of health in the wider and creative sense which we have long advocated The incorporation within the academic sphere of the social services dealing with maternal and child health provides

at once a large field for the training of the student and nurse on this fundamental side of health, and for the initiation, for the first time under the auspices of the schools, of a study of a wide range of questions of national importance. This matter we shall discuss later.

It is important at the outset to define the position of the medical officer of health. As chief medical administrator of the health authority, he is responsible for the public medical services of the area, and he must exercise a directing part in the new planning, with, on the clinical side, the expert help of the professors Further, both on the medical and the sociological side, his knowledge and experience would be utilised on questions relating to teaching and research. He might with advantage become attached to the teaching staff of the school.

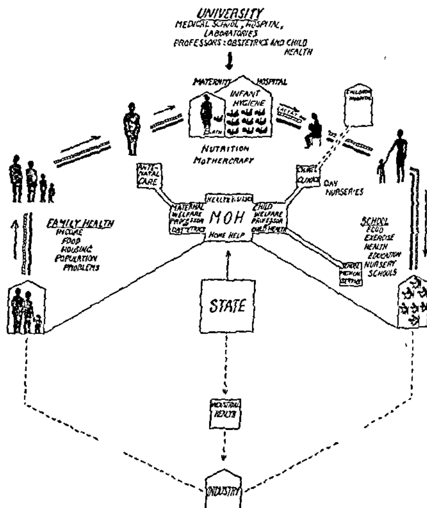
The position of the medical personnel also requires careful consideration In their capacity as teachers in the school they will be engaged at the various clinics and in the school medical service. They will thus be officers under the Local Authority and their appointment will, therefore, be made by mutual arrangement between the medical school and this authority. It is clear that it will be difficult during the initial stages to obtain medical personnel of a sufficiently high standard of training and experience to staff these departments of the medical school Indeed, as we have seen, a main reason for the establishment of institutes of maternal and child health is the failure of the schools in the past to identify themselves with this community movement and to train the doctors and nurses required for its efficient staffing It thus follows that for some years the schools will be largely engaged in the training of their own staff, the professor no less than the others! It is here that we may confidently look to the public services with their many years' experience to provide efficient officers for the new academic posts

The extent to which the medical staff will be on a whole-time or a part-time basis will be determined partly by local conditions and partly by local predilection. It is desirable that some at least of the staff should be part-time and thus be available for the general specialist services of the community.

Functions of the School of Maternal and Child Health

These functions can be conveniently considered under the following headings: the maternity hospital, the antenatal and

child welfare clinics, the school medical services, the social services, nutrition, and the hospital for diseases of children. An attempt has been made to exhibit these activities in the accompanying diagram.



The School of Maternal and Child Health

Diagram showing how this is based upon an integration of the University Medical School and the Maternity and Child Welfare Services of the Local Authority.

The Maternity Hospital.—The maternity hospital, with its associated antenatal and postnatal clinics and with its vast and largely untapped resources for teaching and research in infant hygiene and for the study of the causes of still-birth, prematurity and neonatal mortality, will occupy a key position in the scheme.

It will preferably be associated with a general hospital, which alone provides the intimate collaboration with the medical, surgical and the well-equipped pathological and other services that is desirable at all times and which is of special importance for teaching and research. The maternity hospital will be the common meeting-ground for the teachers of obstetrics and child health. The study of the child must begin with the study of the mother during pregnancy and, after birth, the welfare of the mother determines in an important degree the welfare of the child during lactation and later in its life. Maternal and child health are indivisible and the professors of both subjects must collaborate over a large common field, including nutrition, mothercraft and the various social services that relate to family health and stability.

The Antenatal and Child Welfare Clinics—Under existing conditions these are regionally distributed over the Local Authority area, some in association with the hospital, the remaining and larger number being placed to suit the convenience of the mother. In future planning these must all be co-ordinated under the two professors. In this way there will be achieved the unity of control that has long been desirable in the interests of the maximum clinical efficiency, and that is now essential for the activities of teaching and research. It has been suggested that in future the antenatal and child welfare services should be transferred to "health centres" and carried out under the general practitioners of the area Whatever the ultimate decision on this question, there will remain the necessity for such clinics for teaching under the auspices of the university or medical school and distributed according to the local needs as determined by the health authority

Further, there would seem to be no doubt that the evolution of maternal and child care on a collective basis has followed a rational course. A collective health service implies the provision by the community of those consolidated facilities—medical, nutritional, social, educational, etc.—which are essential to health and which its individual members are unable in whole or in part to provide for themselves. The public welfare services fulfil these terms as is evident from their manifold activities · increasing hospital provision for maternity, the municipal salaried midwife service, the antenatal and child welfare clinics and the school medical service, public arrangements for the feeding of mothers and school children, the provision of day and residential nurseries

and nursery schools, the provision of home help, and other social services. It can be contended with reason that there resides within these public schemes the only effective method for mobilising for mother and child all the social facilities that are a dominating factor in health. It is the conviction of the present writer that to disrupt this natural development at any part—for example, by removing the antenatal from the general maternal care or by undermining the collective value of the school medical service—would tend to break the continuity of health supervision in a sphere where it is appropriate and desirable. At the same time it is equally true that the effective medical service of the area demands a co-ordination between its various elements, and that the maternal and child activities of the Local Authority must be integrated with the services of the general practitioner and the nurse in relation to the family, as well as with the specialist and hospital services, etc. If the general medical services of the future are, as seems possible, planned on a regional basis, we may look forward to the closer general integration that is essential for effective work.

The School Medical Services.—These will be co-ordinated under the professor of child health. The child during school age will thus be brought for the first time under a suitable scheme for teaching and for the academic study of those influences, nutritional, educational and social, that are concerned with the creation and maintenance of health during a critical period of child development. It has frequently been pointed out that to reach their maximum efficiency these services must be greatly expanded.

Social Services.—Throughout this communication and elsewhere we have insisted that just as health is and must be a social ideal, so the methods by which this ideal is to be achieved are in the widest sense social and collective. Only in so far as the schools become inspired and pervaded by this ideal can they fulfil their great new function as servants of the community. As we have long urged, in maternal and child health they have a sphere which imperatively claims the exercise of this function.

We have seen that, by becoming public health officers, the professors become at once professors of " social medicine." They move from the restricted field of the hospital and its clinic, where their observation is fleeting and fragmentary, into the wider environment, where the study of those influences (nutritional, industrial, etc.) which operate on the lives of the people becomes

more vivid and effective. The professors will become concerned with social diagnosis and with social treatment. It has been urged against the public medical officer that his function has often ended when he has filled up and signed his monthly or yearly returns and has watched them being filed on a dusty shelf. Under the new status which we envisage for him he must be endowed with a greater power to guide social health policies. The health returns of the public medical officers have consistently shown a mass of preventable disease and disability in large groups of the people—in the pre-school and school child, in mothers, in army recruits, in industrial workers, etc. But the medical officer, whilst conscious of the social diagnosis, has often been powerless to prescribe the social treatment, and this has gone by default This, as we have seen, has been partly due to the failure of organised medicine to establish its claims in the social field and partly to the limitations imposed on the effective expression of expert medical opinion on the social causes of ill-health As these are generally related to matters which call for centralised action, there is need for the establishment of an *advisory body* to guide the Government on social questions affecting national health and containing prominent representatives from the social field of the various interests concerned—nutrition, maternal and child health, industry, housing, medical education, etc

Amongst the social health activities of the centre organised for the teaching of the doctor and nurse an important place will fall to *mothercraft*. This involves the education of the mother in regard to her own and her child's health and in the importance of maternal responsibility. Amongst other subjects are *home help, day and residential nurseries and nursery schools, convalescent centres for mothers, health education at school,* etc It is, further, clear that *family health* and all that this connotes—income, food, housing, number and spacing of children, etc —has a direct bearing on maternal and child health. The organisation of the social services under combined University-Local Authority auspices will also encourage the study of those problems of *population,* which are of such grave and immediate significance to the country For many years the Local Authorities have accumulated an immense amount of data on these and cognate social subjects Thus they have records of all births and the subsequent physical and mental career of the children through infancy and up to and including school age, and through their health visitors and clinics they have acquired much information regarding family life

Continuity of Health Supervision.—A major advantage of a co-ordinated and collective service is the continuity of health supervision which it offers. The supervision provided by the maternity and child welfare services stretches in an unbroken sequence from the antenatal period of the child's career right up to school age, and each stage is documented in the files of the health authority. There can be no doubt that to this continuing supervision expressed in the care of the mother before and during birth, and of the mother and child in the subsequent postnatal period, must be ascribed one of the major influences in the declension of the maternal and infantile death-rates during recent years. It is desirable that in any new planning this continuity of supervision should be maintained. At the same time it has to be admitted that in the past the advantages thus inherent in our collective health supervision of mother and child have often been more theoretical than effective, and that the new planning should seek to create a system by which their realisation will be more fully achieved. Thus it is of importance that the present breach in the continuity of health supervision when school age is reached should be removed, and that during school age itself there should be built up a more efficient collective control Further, it is clear that the health records of mothers and children in the possession of the public authorities, and which have been built up over a considerable number of years, contain valuable information for the study of health trends and of the influence of varying medical and sociological factors on maternal and child well-being. The valuable purpose to which these data can be put for a demographic study has been well exemplified by the recent investigations of Burns (1942) For the most part, however, these records, containing information of such supreme value to students of health movements, have remained unused and wasted. The establishment of well-equipped institutes for maternal and child health will do much to remedy these defects in the existing machinery and will provide centres adapted for the regional survey of health conditions and movements throughout the country.

Nutrition.—This is the most important single factor in regard to the physical and, as many believe, the mental welfare of the mother and child. It is unnecessary to emphasise the importance of an adequate diet for the nursing mother and for the child at all stages of its development. Within recent years the investigations carried out by Utheim-Toverud (1939) in Norway, by Ebbs,

Tisdall and Scott (1941) in Toronto, and by the People's League of Health (1942) in London have proved the critical importance of a sound maternal nutrition both for mother and infant.

It is important to appreciate that nutrition involves two separate and distinct problems. In the first place there is the study of food values and food requirements and the extent to which the dietaries of different classes of the population are sufficient for health and vigour. This aspect of the subject is, in a sense, academic and is specially suited for consideration by the medical schools. The second side of the question is essentially one for statesmanship and involves those large matters of policy, governmental and financial and economic, which must concern themselves with the ensuring for all classes of the people of a minimum nutrition for health. On the first of these two questions we possess much and, on the whole, reliable information. In general it may be stated that the standards necessary for health are well established. At the same time it is known that before the present war the diet of about one-third of the population was insufficient for health, and that in large measure the state of nutrition was directly related to economic status (Orr, 1936) It is specially relevant to our present subject that the majority of the children belong to the underfed classes. It is known that the children of the poor in general exhibit a lower state of physical and mental development and a lower resistance to disease than the children of the more favoured classes. The appreciation of the cardinal importance of nutrition in the production of these social differences in health dates largely from the observations of Corry Mann (1926), quickly confirmed by other workers, that poor children when placed on a good diet exhibit an increase in weight, height and vigour similar to that of the higher social groups. From these observations there has grown up the conviction that the imperfect health and developmental defects widespread throughout the people of this country are due in high degree to the poor environment, especially in regard to nutrition, in which many of the children and adolescents are reared. These are all matters that must engage the unremitting attention of the medical schools and, in a special degree, the centres for maternal and child health. The doctor in his corporate capacity is not concerned with those issues of a politico-economic nature, with their complex national and international ramifications, that lie behind the provision of a good diet for the people At the same

time, as guardian of the nation's health, he must insist that this great task can no longer be evaded.

The Hospital for Children's Diseases.—Whilst the main function of the centre is the study and teaching of those principles that are concerned with the creation and maintenance of health, the school must provide hospital facilities for those children who require special medical care, and for the completion of the training in this important side of the child problem for students, doctors and nurses. We need not enlarge on the important part played by the children's hospital in the early diagnosis and treatment and restoration to health of large numbers of children each year. Further, through its convalescent homes and rehabilitation centres, it provides extensive facilities for the training of doctors and nurses in important branches of child health. Moreover, the experience of the children's hospitals is of paramount value in the unique opportunities it has of studying special forms of "collective disease" and of thus directing the specific lines of investigation in regard to collective and social health.

Finally, whilst this communication has been specially concerned to outline the policies required for the establishment of schools for maternal and child health, these policies are capable of being applied with advantage in the non-academic field. The writer is convinced that in every Local Authority area the maternity and child welfare services should be organised on a collective basis and should be administered and staffed by the most experienced personnel available locally. This would improve the efficiency of the services and it would at once identify the local obstetricians and pædiatricians with one of the most important sides of maternal and child welfare, namely, that directed to social health.

Summary

1. From the standpoint of health the mother and child constitute a *biological unity*.

2. In the planning of the future health services it is necessary to make arrangements for the training of the doctors, consultants, nurses, health visitors and social workers who will be responsible for maternal and child welfare.

3. These arrangements include—

(*a*) The establishment of adequate departments of maternal and child health in the medical schools and *universities*.

(*b*) Intimate collaboration between these departments of maternal and child health and the maternity and child welfare and school medical services of the health authorities.

4. The creation and maintenance of maternal and child health requires collective enterprise and effort. It cannot be considered apart from other aspects of social health, for example, those relating to the economic security of the family, industrial health, etc. Further, to be fully effective the various medical and social services on which it is based must be so organised as to provide a continuity of supervision from the prenatal period to school age.

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MODERN TRENDS IN PREVENTIVE AND SOCIAL ASPECTS OF TUBERCULOSIS

By CHRISTOPHER CLAYSON, M.D., D.P.H

THE decline in the mortality from tuberculosis has been one of the most remarkable epidemiological changes in modern times In 1882 the death-rate from the disease in Scotland was 311, in 1912 it was 172 and in 1939 it was 69 per 100,000 of the population. Or alternatively, sixty years ago tuberculosis accounted for approximately 16 per cent. of all mortality and was the most outstanding cause of death, whereas now it causes about 5·5 per cent. of deaths and ranks only fifth on the list of fatal diseases. Figures for England are similar but need not be quoted, since this survey deals more especially with the situation in Scotland.

The Causes of Decline in the Mortality from Tuberculosis.—Such a striking change in mortality must of course have numerous causes Some of these causes are of general application, since they operate to produce a diminution in all types of sickness and to improve the health of the country as a whole Others are of more special relationship to the tuberculosis problem itself. The *general causes* in the decline in the mortality from tuberculosis are tied up in the improvement of the standard of living and education, which became evident in the latter half of the nineteenth century with the gradual increase in the level of real wages. There was a general interest in health problems coming to life which was shown in the creation of the Local Government Board in 1872. Gradually matters improved further until the passing of the National Health Insurance Act of 1911, and the general establishment of wider health services.

But all this does not explain why the death-rate from tuberculosis should have fallen so much faster than the mortality from all causes of death during the past thirty years or more. The reasons for this particular phenomenon are to be found in the more *special causes* in the decline of tuberculosis. Some experts believe in the epidemic theory, holding that we are witnessing

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the end of an epidemic of tuberculosis which has lasted between 150 and 200 years. Others believe the genetic theory which states that the decline is due to the elimination of susceptible elements from the population, leaving the more resistant strains to defeat the disease. Yet others observe that the trend in mortality is due to the activities of the anti-tuberculosis services, which have caused a decline in tuberculosis greater than could otherwise have been expected.

It is no part of our task to disentangle the evidence on which each of these viewpoints is based. We are more especially concerned with the examination of the part played by the anti-tuberculosis services of the community. For tuberculosis is still a great problem, and we have to ask ourselves whether the same machinery which has played a part in diminishing the death-rate from tuberculosis from 172 in 1912, when the organisation was established on a national scale, to 69 in 1939 will be adequate further to diminish the mortality to, say, 15 per 100,000 in 1970. This question, which was already engaging the attention of tuberculosis workers in peacetime, has become of even greater urgency in war, for the death-rate is now back to where it was ten years ago.

I propose, therefore, that we should consider the following aspects of the tuberculosis problem :—

1. The General Requirements of the Country in combating Tuberculosis.
2. Critical Review of the Tuberculosis Scheme.
3. Probable Future Developments

I. The General Requirements of a Country in combating Tuberculosis

Any infective disease, but especially a chronic infective disease like tuberculosis, presents two groups of problems, one purely medical and the other both medical and social. There is no need to elaborate them unduly They may be summarised as follows :—

The medical aims must include provision for diagnosis and notification of all cases. Specialised treatment must be made available for those who can be cured (arrested), and general medical supervision for those who can not.

The medico-social requirements should include those

measures of help which are not purely medical and may be termed the "care" of the tuberculous subject and his family. Such provision should also facilitate the management of that difficult period in which the patient returns to his occupation. Again, measures must be operated to prevent the spread of infection, whether of human or bovine origin.

II. Critical Review of the Tuberculosis Scheme

We must now outline the functions of the different units of the Tuberculosis Scheme, and examine their mode of operation in order to ascertain to what extent they may fall short of meeting the national requirements as summarised in the first section of this review. It should be made clear, however, that any imperfections which may exist in a tuberculosis scheme do not by any means reflect on the medical and nursing personnel engaged in that important work. Some defects are inherent in the present legislation. Others are simply bound up in the question of expense. As in many other matters, if results are to be gained money must be spent, and we cannot expect a local authority which can spend only, say, £40 per 1000 population per annum on its tuberculosis scheme to provide a service comparable in structure or results with an organisation costing, say, £200 per 1000 population per annum.

It is convenient to examine the different units of the tuberculosis schemes seriatim

1. **The Dispensary.**—The functions of the dispensary which is an out-patient institution are firstly to examine suspects, notifying those proved to be tuberculous to the health authorities, and to arrange for suitable treatment; secondly, to examine contacts of these cases; thirdly, to exercise general management including domiciliary supervision of all cases not in hospital; and fourthly, to carry out measures of popular education.

In general, it may be stated that the dispensary which is the pivot of the whole tuberculosis organisation has served its purpose with great success. Its efficiency, however, depends to some extent on the ease with which its activity may be established in any given area.

The Dispensary System in Rural Districts.—The tuberculosis problem in country districts is somewhat different from that encountered in towns. The death-rate is usually much lower, approximately 30 to 50 per 100,000 in most of the lowland

counties, as compared with 60 to 80 per 100,000 in the towns. An important exception to this low rural death-rate, however, is to be found in the Highlands and Islands of Scotland, where the death-rate is still between 80 and 100 per 100,000. But whether the rural mortality be high or low a variety of factors operate to make further progress a matter of some difficulty Tuberculosis services are much more readily organised in towns than in the country, and townspeople avail themselves more readily of the health facilities provided than country people.

The dispensary practice in the country has never reached the level established in towns, nor indeed can it be expected to do so. In thirty-one Scottish counties only eight have tuberculosis dispensaries. This does not mean that the tuberculosis problem is neglected in the remaining counties, but it does mean that the peculiar conditions under which the rural tuberculosis officer works place him at a disadvantage as compared with his opposite number in towns, since he does not have at hand the full resources of a dispensary including X-rays. An endeavour is made to have radiological examination carried out by agreement with any small hospitals in the area which may be so equipped, but early diagnosis, frequently so difficult at the best of times, is still more difficult in country districts, no matter how expert a clinician the tuberculosis officer may be or how wise the general practitioners in his area.

But even in urban dispensaries difficulties arise. One of these is the *examination of contacts*. Many dispensaries achieve a high percentage of contact examinations, but many others are not so successful, so that results for the various regions of Great Britain indicate that approximately only half the contacts are examined The best results are of course in the big towns, where not only one examination but repeated examinations are commonly carried out Ideally, of course, this type of investigation should not only include the family but also those in contact with the patient at work. Here, however, a very real difficulty arises, and clearly it is not possible to persuade a whole workshop staff or business concern to undergo contact examination as at present conducted because one of their number has developed tuberculosis. The solution of this difficulty is already apparent in the evolution of mass radiography and will be referred to again.

2. **The Sanatorium.**—In arranging for suitable treatment the medical officer of the dispensary sends those patients in

whom arrest of the disease may be expected to the sanatorium. This is the institution for curative treatment based on raising the natural resistance of the tissues and by the specialised methods of modern therapy.

We have already noted how the organisation of dispensary services differs in rural and urban areas. In studying the requirements for institutional treatment the same observation may be made. There were in peacetime 5500 institutional beds for the accommodation of tuberculous patients, and experts (Committee on Scottish Health Services) held that the number was reasonably adequate to meet the country's needs. But many of these beds were distributed in various parts of the country in small hospitals of less than fifty beds; and whilst doubtless excellent in their own way, and quite efficient as long as treatment of tuberculosis consisted of fresh air, rest and graduated exercise, they were of less use in meeting the needs of the present day, being neither equipped nor staffed to carry out the modern treatment of tuberculosis. Thus certain parts of the country are not so well provided for as they might appear to be purely from the point of view of numbers of beds

The average sanatorium has failed to develop so far as it might the *employment of patients* along useful lines. Occasional maintenance and repair work and the development of handicraft hobbies are useful from a psychological standpoint, but are not enough. What is needed is a more serious effort at organised and sustained work as a prelude to rehabilitation. This is no new conception. It is supposed to be an essential part of sanatorium routine, but relatively few sanatoria are as yet equipped with the necessary workshops and staff to put the precept into practice

3. **The Hospital.**—Patients more seriously affected, for whom only temporary amelioration may be possible, and perhaps not even that, are provided for by admission to the hospital. Treatment is by raising resistance and by symptomatic measures. The aim is to provide prolonged and, as far as possible, continuous care of these cases and, since they are usually the more infective types, to aid in preventing the spread of infection.

Of the 5500 beds available in peacetime in Scotland, it does not appear from the published data how many are at our disposal for the special care of advanced cases Indeed, in small authorities it is manifestly impossible to separate early and advanced cases into different hospitals Nevertheless the reasons for such

separation wherever practicable remain sound. The sanatorium must be equipped and staffed for many types of treatment, and yet contrive to combine with such treatment open-air conditions a little more rigorous—though not to the degree thought necessary in former years—than those usually considered advisable for advanced cases. Again, where both types of cases are mixed, the interchange of mental reactions when advanced cases see early cases recovering after receiving special treatment, and when early cases see advanced cases so frequently losing ground, exerts unfavourable effects on both.

But even when hospital segregation of advanced cases is practised it is not altogether possible to carry out completely the functions assigned to it. So many of the available beds are required for the treatment of early cases that the accommodation available for prolonged care of the advanced cases is limited For advanced cases commonly require unusually prolonged treatment and the number of beds desirable to provide adequate care for them would be very large. But the number of beds needed to go a stage further than treatment and to effect, by means of segregation, the prevention of the spread of infection is quite beyond the existing scope of the institutional provision for advanced cases.

In this connection it should be emphasised that at the present time only 40 per cent. of fatal cases of tuberculosis die in hospital. In large towns of course the proportion is higher, but in country districts and small towns only 10 to 11 per cent of deaths occur in hospital. How many of these were accommodated for any length of time before death we do not know. But we do know that for the year 1941 in Scotland as a whole as many as 37·7 per cent. of fatal cases of pulmonary tuberculosis were notified only three months before death, or even after death, or even not notified at all, and 27·7 per cent were notified only one month before death, at, or after death. So even if beds were available for the segregation of cases, more willing notification is needed to make such a procedure practicable.

But there is another real difficulty Many sufferers in a chronically infective state have to be discharged from hospital to make room for others more seriously ill. They in turn suffer a relapse sooner or later and must be readmitted. In due time they improve again and, conscious of improvement, seek their discharge with or without medical sanction. In this way chronic cases may come in and out of hospital many times. The hospital

increases their expectation of life and also indirectly their opportunities to spread infection.

It seems permissible to conclude that the hospital as a unit of the State tuberculosis services has not yet been developed as it might be either for the care of advanced cases or for the prevention of the spread of infection.

4. **The Colony.**—The first colony for tuberculous subjects was established as part of the Edinburgh Tuberculosis Scheme in 1908. Another was developed at Hairmyres in Lanarkshire. But the official services of Great Britain have never developed colony work to any great extent, and it has been left to voluntary endeavour in England to demonstrate fully the value of the tuberculosis colony.

The underlying conception in colony work is that the treatment of the tuberculous subject does not cease when the needs of specialised medical therapy have been satisfied and the patient has been discharged from the sanatorium. Treatment, using the word in its broadest sense, must continue till the patient is not only fit for work but is firmly established in work.

The two best-known colonies in the country to-day are at Preston Hall in Kent and at Papworth in Cambridgeshire. Their procedure does not call for a detailed description in this general review, but may be summarised as follows. Patients in whom there is a reasonable prospect of arrest may be admitted to the colony almost at any time in the course of their recovery, if necessary to the sanatorium unit to complete medical treatment. When in the judgment of the medical staff they are fit to resume work they do so in the usual graded manner. When they are able to work, say twenty hours per week, they receive a certain weekly sum for pocket money. When they can carry out full-time work they are absorbed into the settlement staff and receive trade union wages. The method has attracted patients from the more progressive local authorities, and in such cases the charge on the local authority steadily diminishes as the wage-earning capacity of the patient rises.

The trades involved have so far been chiefly the manufacture of portable buildings, fancy goods, travelling equipment of all kinds and other leather work. It is interesting to observe also that printing is one of the major occupations developed in the tuberculosis colony. Under ordinary conditions tuberculosis in the printing trade is significantly in excess of normal. The comparative mortality figure for tuberculosis, based on 100

standard deaths between the ages of twenty and sixty-five years, is 128. Yet, under colony conditions printing is a healthy trade.

When the patient has completed a term at his trade to the satisfaction of the medical and industrial officers he is provided with a house at a reasonable rent and may be joined by his family, members of which may also find employment in the settlement.

This method of rehabilitation is suitable for all cases who reach the necessary standard of fitness, but especially for those who nevertheless may be infective for a considerable period.

The development of colony work, whilst it became notable in the voluntary field, more especially under the guidance of the late Sir Pendrill Varrier-Jones at Papworth and Dr J. B McDougall at Preston Hall, has not yet been taken up on an effective scale by the official tuberculosis services. Only in Nottinghamshire and Cheshire have such steps been taken, but the war has prevented further progress. The State has yet to fulfil its responsibilities in safeguarding the return of the physical worker to industry.

Possibly the first step in State interest in this work is to be found in the publication of Circular 2576 by the Ministry of Health. This document stated that the Ministry of Labour Scheme for the resettlement of disabled persons was to include not only those disabled through war or industrial accident, but also those disabled through tuberculosis. Unfortunately the proposed scheme is only to apply to those sputum negative cases already fit to be employed in normal industry These cases of course represent a minority who are least in need of rehabilitation. It is, however, a modest start. Future developments will be considered in the next section.

5. Care Work.—Assistance to patients not directly concerned with diagnosis and medical treatment, but which consists in avoiding economic difficulties may be called care work In its widest sense the State may be said to provide for this aspect of the problem under the National Health Insurance Scheme, and under Public Assistance measures As originally defined, however, care work refers to help where need exceeds the possibilities of statutory provision It has received most attention where voluntary and official workers combine under the title of *Care Committee*. They devote themselves to many matters which the average tuberculosis officer has not time to overtake

personally, much as he would like to, namely, eliminating housing difficulties, seeking suitable re-employment, providing clothing and bedding, and in solving a variety of economic problems.

In this analysis of the operation of the tuberculosis services of the country it has to be admitted care work has not developed to the level it deserves—particularly in Scotland. Out of fifty-five tuberculosis schemes operating in the counties and burghs of Scotland only five have Care Committees, and some of these are synonymous with the Public Health Committee, which means they are not Care Committees in the real sense of the term. It seems that care work in England is much more active. It has of course the great advantage of statutory support under the Public Health Act of 1926. If a local authority in England wishes to develop care work it can obtain a statutory grant of money amounting to £2 to £5 per 1000 of the population per annum, and endeavours to raise at least a similar sum from local charities. The Care Committee, consisting of official and voluntary workers, becomes a financially autonomous body which can help sufferers along lines already indicated and without working to a fixed income scale in assessing needs.

But even the most willing and wealthy Care Committee cannot overcome difficulties on the scale needed. Only *the State* has adequate resources for the purpose. Under the present scheme of National Health Insurance the patient is entitled to free institutional treatment. If this lasts for more than six months—as it usually does—the patient receives on his discharge disablement benefit of 10s. 6d. weekly, supplemented by such extra assistance as may be available How the tuberculous subject can maintain health on this standard cannot readily be explained. Indeed, National Health Insurance is defective in combating prolonged sickness. This unhappy position affects the tuberculous patient in two ways. It leads him to continue working long after he should be undergoing treatment, and likewise induces him to resume work before he is fit to do so Tuberculosis physicians are confronted with the problem of advising which is the smaller danger, to live at home inadequately or to return to work unfit.

The conclusion is inescapable that despite the valuable work of official and voluntary organisations the care of the tuberculous subject, *i.e.* that part of his supervision not directly connected with diagnosis and medical treatment, is seriously defective under present legislation.

Summary.—It is not claimed that this is a complete critical

survey of the tuberculosis services of the day, but the imperfections noted may be summarised as follows :—

1. Early diagnosis leaves room for improvement, more especially in rural areas. Family contact examination can be improved. Occupational contact examination remains to be achieved.
2. The best treatment is obtainable only in the larger centres. Facilities in rural areas have not been evolved to best advantage.
3. Further development is required in provision for advanced cases.
4. Treatment is not followed by rehabilitation.
5. Care work in tuberculosis is inadequate.

III. Probable Future Developments

The statement was made in the introduction to this lecture that the National Tuberculosis Scheme which has played a part in diminishing the seriousness of the tuberculosis problem in the twenty-eight years or so following its inception in 1912 would not be adequate to ensure the same rate of progress as a long term policy after the war. In the year or two immediately following the return to peacetime conditions there will probably be a sharp drop in the mortality, until the position is reached which would have been arrived at in the course of a normal uninterrupted decline. But from that point onwards, if we are to look for accelerated progress, we must anticipate certain changes in the tuberculosis services of the country, and we may now consider the general improvements which are to be expected.

1. **The Dispensary.**—We have noted already the difficulty of what may be called occupational contact examination as distinct from family contact examination. This question will be one of those solved by *mass radiography* We need not pause to consider the technical aspects of the procedure by means of which very large numbers of people may be investigated in a very short time and at relatively low cost. But the preliminary results and their implications are very striking. Traill (1942) has shown that out of 32,128 members, male and female, of the Royal Air Force personnel between the ages of eighteen and twenty-four years, 179 or 0·56 per cent., were the subjects of pulmonary tuberculosis ; of these 94, or 0·3 per cent. of the total, were the

subjects of active lesions. These lesions have occurred in a specially selected population, and the proportion of lesions in the general population of the country in the same age group will be higher. But even taking the figures as stated, we may infer that there are among the population of Scotland between eighteen and twenty-four years of age at least 2200 unsuspected cases of tuberculosis. What the figures are for the population of 2,330,000 between the age groups of fifteen and thirty-four we cannot state definitely, but the figure may well amount to 12,000 unsuspected cases, of which something over half are active.

Presumably the employment of mass radiography to discover these cases will be organised on a voluntary basis in business and industry, and also as a pre-requisite to employment. Even with propaganda, however, it seems doubtful whether the procedure could ever be complete without some measure of compulsion For this reason we may expect that the normal evolution of mass radiography will see it incorporated in the final school medical examination and thereafter practised at intervals in adult life. In this way the majority of cases will be discovered while still curable, and the first general requirement of the country in combating tuberculosis will be fully met.

Subsequently the more complete medical investigation and supervision of these cases will lead to a very great increase in dispensary work, domiciliary visitation, and family contact examination. But there can be little doubt that by periodical, possibly annual mass radiography the era of certainty in early diagnosis will be brought very much nearer.

But when mass radiography is extended to country districts it will raise difficult problems, for in these areas dispensary work is difficult enough already. The nature of the investigation will require a mobile unit, and the follow-up of cases will once again raise the question of merits and demerits of *mobile dispensaries*, especially in those counties where the dispensary system is not already operative as such. Mobile dispensaries in rural areas have never found much favour in this country as they have done in France or in America. But it seems clear that one of the consequences of mass radiography will be to focus attention once again on the problems of organising anti-tuberculosis measures in rural districts.

2 **The Sanatorium.**—The limitations already described in connection with sanatorium work have led to the suggestion that a scheme of *regional planning* is needed to ensure that all cases,

from whatever part of Scotland they may come, be efficiently provided for. Broadly speaking, the scheme envisages the establishment of large fully equipped and expertly staffed regional centres, each serving a precise area of the country. The patient, possibly after a preliminary period in a local institution, would be admitted to the regional centre for such specialised treatment as might be considered necessary. He would then return to the local sanatorium to complete his convalescence, or better still be passed on to that part of the regional scheme which we may venture to hope will provide for rehabilitation. The consideration of rehabilitation, however, will call for further comment in another section.

When originally considered the scheme of regional planning for sanatoria was thought to be adequate in meeting the country's needs were it based on the re-organisation of the peace-time 5500 beds. Since then, however, the prospect of the development of mass radiography with expected improvement in early diagnosis, and the general increase in tuberculosis due to the war has brought new responsibilities in the matter We are not here concerned with immediate war-time needs. The post-war situation will evolve gradually But once mass radiography is established we must prepare for an annual increase in the numbers of sanatorium beds. What this number will be no one can tell without further experience.

The scheme of regional planning would appear to complete the second main requirement as outlined in Part I of this lecture, namely, the curative treatment of all cases in whom arrest of the disease may reasonably be expected.

3 **The Hospital**.—As the campaign against tuberculosis improves its efficiency and draws near the complete control of the disease, the first unit of the organisation to call for gradual liquidation will be the hospital for advanced cases. But that is looking far ahead. Provision for these cases will remain a necessity for many years, and could with great advantage be extended until the vast majority of deaths from tuberculosis occur in hospital This is one of the great difficulties in tuberculosis work The problem is to encourage patients to take advantage of the prolonged residence in hospital in their own interest and in the interests of public health Compulsion in this matter has so far proved unsatisfactory in all but the most exceptional circumstances.

Two factors will help in promoting prolonged hospital

segregation and we must look for their development. Freedom from economic worry will go far to help in this as in other matters (see below under "Care Work") by relieving the patient of the *anxiety of providing for his dependents and otherwise by making* it worth his while to undergo institutional treatment.

Again, it should perhaps be emphasised that the amenities of the hospital for advanced cases deserve even greater consideration than the amenities of the sanatorium, since the average duration of stay is longer and since hospital patients do not usually have the mental satisfaction of receiving specialised treatment. Palatial quarters are not needed, but agreeable surroundings are even more important for the hospital than for the sanatorium. Occupational therapy should of course be instituted, though it is doubtful if true vocational training could be actively followed to any great extent. There is still a wide field for progress in the institutional care of advanced cases

4. **The Colony: Regional Planning for Rehabilitation.**—*Just as the State adopted the dispensary* system for tuberculosis after it had been proved by voluntary endeavour, so it will adopt rehabilitation schemes now that the great English colonies have proved themselves both sound and practicable. Already the more enterprising authorities, as we have seen, have collaborated with the voluntary organisations concerned, and what is now needed is the provision for carrying out rehabilitation on a national scale. English experts conceive a scheme of regional planning for rehabilitation, in which the country could be divided into six regions co-ordinated by a central board. In Scotland the need is similar, though of course six regions would be quite unnecessary. It seems that any such scheme of regional planning for rehabilitation should be co-ordinated with the region for specialised treatment. In such circumstances two or three regions would possibly satisfy the needs of Scotland provided that occupational training were developed to a greater *extent in* certain existing sanatoria.

It is necessary to formulate some idea of *the number of cases for which rehabilitation will be needed* in Scotland. For this purpose the general method adopted for England in the Fifth Report of the Employment Committee of the Joint Tuberculosis Council may be followed. Sputum-negative cases can be ignored for the moment because they form the least difficult part of our problem. Sputum-positive cases are those for which rehabilitation along colony lines is chiefly required In 1941 there were

approximately 8000 such cases known to the Department of Health for Scotland, and the number will of course be increased when mass radiography is developed. Of these a considerable number may be eliminated from the scope of the estimate. For instance, old people and young children are unsuitable for industrial rehabilitation. Similarly, married women may be discounted since their problems are rather the sphere of the Care Committees For the remainder there are approximately 3000 males and 1600 unmarried females between the ages of fifteen and forty-five who have positive sputa Of this number about one-third will be at any given time purely medical problems, either because they are undergoing special treatment or else because they are of bad prognosis. The remaining cases, which in Scotland at present number about 3000, are the special field for rehabilitation.

For Scotland to cater for this number of infective cases on colony and settlement lines would be a formidable undertaking. Short of compulsion it is doubtful whether colonies would be more than a partial solution to the difficulty. It should be noted, however, that in England 75 per cent. of cases who have had a period of residence in a sanatorium attached to a village settlement are willing to join the community if vacancies are available. This is indeed a great achievement; but it seems that even with well-developed settlements there will always be a considerable number of infective cases requiring direct rehabilitation into industry, and their supervision becomes part of the wider care work in tuberculosis

5. **Care Work.**—The increasing part the State is going to play in the care of the tuberculous is especially evident in the attention that is being devoted not only in colonies as outlined above, but also by *non-institutional methods*. So far as the latter are concerned it seems that patients may fall into three categories, those fit for work under ordinary conditions, those fit for part-time work, and those fit for sheltered work

The Inter-Departmental Committee on the Rehabilitation and Resettlement of Disabled Persons has recently made certain proposals which would apply (amongst many other categories of disablement) to tuberculous subjects *fit for work under ordinary conditions* If this scheme were to become operative, and if tuberculous subjects wished to avail themselves of it, employment would be made available on the quota system. Certain employers, selected on the basis of numbers employed in their establishments,

would be encouraged to engage a quota of "disabled" persons on their staffs under the general administration of the Ministry of Labour and National Service through local committees. This would be a great help in re-establishing the employment of the more readily employable cases.

Tuberculous subjects fit for *part-time* work would require a system of graded return to industry. In such a scheme the number of working hours would be shortened, but work would be carried on under ordinary industrial conditions. It seems probable that the system would apply more especially to those non-infective cases who were not quite fit enough for full-time work. To ensure the effectiveness of such a scheme, State aid would be needed in the shape of subsidised wages in order to maintain income at the normal level.

Thirdly, those who are only fit for modified work should be provided for in schemes of *work under sheltered conditions*. The greater proportion of these cases would probably be sputum-positive. These subjects are ideally provided for in colonies and village settlements, but, as we have seen, it is unlikely that accommodation will be available for all such cases in these organisations, and still less likely that all cases would avail themselves of such facilities. This is the most difficult of rehabilitation problems in tuberculosis, but it has in America and Russia been overcome in some measure by specialised workshop facilities, particularly in relation to manufactured goods. With suitable aid from the Government and local authorities concerning orders for articles in constant demand for their own purposes, it seems that the economic difficulties both of residential colonies and non-residential workshops for the tuberculous would be overcome

Increasing State interest in care work, however, is by no means restricted to rehabilitation of chronic or of arrested cases. At the very beginning of treatment great changes are also taking shape. The Minister of Health has already announced the principle of *allowances for the dependents of patients* who have to undergo treatment "which is in the interests of public health as well as their own." Details of administration in Scotland are at present being worked out by the Department of Health. We may hope, however, that the word "treatment" in the Minister's statement quoted above includes out-patient supervision by a tuberculosis officer as well as residential treatment in an institution. In this way the great difficulty of patients requiring to return to

work too soon will be overcome, and they would at last be able to take full advantage of the treatment provided.

The above are examples of growing interest and probable direction of State-aid in care work in tuberculosis, but all the financial problems involved are attracting the attention of experts. The precise details of any improved scheme of State economic help cannot be within the knowledge of the individual commentator, and must in any case depend on post-war economic conditions, but in general terms the requirements may be summarised as follows :—

1. There should be a basic disablement benefit payable to the patient until he is able to resume work (on a part-time basis if need be), or until he is deemed permanently unfit for work.
2. The disablement benefit should be suitably increased to make provision for the varied needs of the family unit (*a*) whilst the patient is in hospital; (*b*) after his discharge so long as he is unfit for work and under the supervision of the tuberculosis officer; and (*c*) whilst he is undergoing rehabilitational training in a colony.
3. When the patient is fit for work but a graded return to industry is desirable, a system of subsidised wages for part-time work should be instituted till such time as he is pronounced fit for normal work
4. When the patient is certified as permanently unfit for work he should receive a sickness pension

If the State is to help the patient along any or all of these lines the patient must also help the State. Some increase in the powers of compulsion may be needed should such co-operation by the patient not be forthcoming. In particular, the patient should be *required* to undergo such institutional treatment as is in the interests of public health Also where there is reason to suppose a patient in receipt of special allowances is plainly abusing this type of care by misspent leisure, the possibility of some degree of control must be explored

The Special Problem of Bovine Tuberculosis

We have already noted that in any tuberculosis scheme measures must be taken to prevent tuberculous infection of bovine origin as well as that of human origin.

Magnitude of the Problem.—In Scotland there were in peacetime approximately 1,300,000 cattle, of which about half were infected with the tubercle bacillus. There were approximately 370,000 cows in milk, of which 0·5 to 1·0 per cent. suffered from tuberculosis of the udder and consequently gave infected milk. (Figures for wartime are not available.) It is not surprising, therefore, that between 8 and 10 per cent. of tested samples of milk contain virulent tubercle bacilli. The number of infective doses of bacilli in the containers from which these samples are taken may well be enormous, so that the frequency of human tuberculosis of bovine origin is not surprising. It may be stated that about 400 deaths a year are caused by the bovine bacillus, and that at the present time about 3000 persons suffer from tuberculosis of bovine origin.

The Prevention of Bovine Tuberculosis.—There are two main methods of preventing infection of human beings by bovine tubercle bacillus, namely, treating the milk and treating the cows.

Treating the Milk.—This may be termed the short-term policy, and may be carried out by some form of heat treatment. An approved method of pasteurisation of clean milk is the method of choice, and should be carried out in all large centres on milk which is not already guaranteed free of tubercle bacilli by other means. In rural areas where economic and transport difficulties prevent pasteurisation the milk should be boiled, and intensive propaganda to this end should be instituted.

Treating the Cows.—This may be termed the long-term policy. It aims at preventing bovine tuberculosis in man by eliminating tuberculosis in cattle, and was pioneered in Scotland on behalf of the Royal Victoria Hospital Tuberculosis Trust, by Dr J. C. Simpson of Southfield Sanatorium. The most promising variation of the method yet attempted is what is known as the Attested Herds Scheme which began in 1937. It consists in building up tubercle-free herds on the basis of the tuberculin test. To begin with this is done voluntarily. When a substantial majority of cattle in any given area are free of tuberculosis the remainder may be compulsorily tested, and infected animals destroyed. This would create an attested area which would then be protected from re-infection from outside by controlling cattle movements. Financial encouragement is given in this scheme by providing a bonus on milk sold from such herds. So far in Scotland only about 6·5 per cent. of cattle have

been attested in this way, and obviously the policy, though sound, will take a long time to come to fruition. Meantime, all milk not from attested herds should be pasteurised or boiled.

We must now close this survey, incomplete though it be. But in doing it is fitting to pay a tribute to the memory of the pioneer who began his organisation in Edinburgh in 1887. Sir Robert Philip planned the foundations of his tuberculosis scheme so wisely that no fundamental alteration is needed to carry the superstructure that is now being built over half a century later. He would be gratified, though not surprised, at the developments we see to-day and have tried to foresee for the future.

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SOCIAL PSYCHIATRY

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DURING war-time there is a great increase in community feeling. The general danger not only makes each person realise his dependence upon the group but also increases his sense of responsibility towards the group. This increased community spirit is not just a means of general defence to be discarded as soon as the war is over. People are realising that the individual and the community stand or fall together both in wartime and in peacetime and are realising that there is more sense of achievement in the service of humanity than in the pursuit of selfish, individualistic aims. So there is wide interest in planning and reconstruction both nationally and internationally, that is, in social changes which are to benefit all members of the community.

The human being and the community in which he lives are inseparably bound together, which is but another way of saying that the biological organism and its environment are inseparably bound together. As man cannot be dissociated from his environment, the two must be studied and treated as one. We in medicine may fairly claim that we have long understood this and have preached its meaning for the cure, and still more for the prevention, of disease. The general interest in social medicine to-day is as much the result of our past knowledge as the result of the stimulus of wartime. And one may fairly claim that social psychiatry is an important part of social medicine. An essential part of Adolf Meyer's psycho-biological principles is that a person and his human and material environments are constantly acting upon one another. In 1931 Professor Henderson gave the Morison lectures at the Royal College of Physicians, Edinburgh, taking as his title Social Psychiatry. He has also written on special aspects of the subject, and I am indebted to his teaching for my interest in Social Psychiatry.

The psycho-biological view that man and his environment are

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inseparably bound together keeps one from any extreme attitude. Social reform is not a panacea. While one no longer attributes to the individual all that happens to him, one must not attribute to the community all that happens to its members. There are inherent in human nature and in human life factors not changeable by social means or even by any other known means. To illustrate what is unchangeable: the literary works of the past which have best survived are those describing human thoughts, feelings and life situations which we still appreciate to be real, although the social setting has changed greatly since the writers lived.

The constant interaction and intermingling of individual and of social factors make it both difficult and undesirable to attempt to define rigidly the term Social Psychiatry. One may say roughly that it has five divisions. Firstly, the effect of the mass of psychiatric patients upon the life and health of the community. The psychotic and the mentally defective in institutions are a big burden, but there are bigger ones The great numbers of psychoneurotic patients suffer from much personal unhappiness and social inefficiency. Henderson (1939) has emphasised the problems of the psychopathic states. Among these the alcoholic, suicidal, criminal and sexually perverted types especially form a group which has a most damaging effect socially, and our means of dealing with them are still very inadequate. Secondly, the provision of a complete psychiatric service for the community, including the mental hospital; a special in-patient unit for psychoneuroses and co-operative cases generally; an observation ward for cases of attempted suicide and acute transitory psychoses of all kinds, out-patient departments for adults and for children, and psychiatric co-operation with general medicine in the treatment of patients and with the legal authorities in the treatment of delinquents. Thirdly, the guidance which psychiatric knowledge can give the community in the arranging of its life and activities. By this I mean something even more constructive than direct prophylaxis. I mean advice on the organisation and direction of the life of the ordinary individual, both personally and in the community. A specific example is Rees's description (1943) of selection of officers and men in the Army Rees said: "It has set a standard which will certainly be applied in industry and in social life in the post-war world" Fourthly, the study of general movements within the group—an extension of the so-called "crowd" or "mob" psychology. Fifthly, the investigation of

those social factors—external to the individual—which are causes of psychiatric illness and which might often be prevented or remedied by community action. It is mostly this fifth division which I shall discuss to-day, attempting to mention the principal factors which practical experience has shown to be important. I will deal with these factors as social ones, but from the nature of the factors discussed you will appreciate that personal elements are often as important in their causation as the social elements. Let us take a general view of a person's social life, discussing it under general headings such as the family and the home; work; accidents, diseases and rehabilitation; and let us also discuss some specific psychiatric conditions.

The Family and the Home

The family is the unit of which society is built, as the body is built of cells. Upon the health and security of the family are founded the health and security of the community. The first need is that the family should be founded upon a healthy stock. Heredity is the sole cause of only a few, uncommon psychiatric states. Causation in psychiatry is generally multiple, not single, and heredity is usually important only as a predisposing cause of breakdowns. If an hereditarily predisposed person meets difficulties in his environment, he may break down where others would not. If he does not meet such difficulties, he may not break down. As heredity is so seldom the cause in itself, enforced sterilisation of large groups of cases is unjustified. Henderson and Gillespie (1940) divide the social measures to deal with heredity into two groups—negative and positive eugenics.

Negative eugenic measures prevent the reproduction of poor stocks and are already taken to some extent by the segregation in institutions of the more serious cases. The other negative measures are celibacy, contraception, sterilisation and abortion. These should be applied voluntarily to individual cases, whose family history has been fully investigated and has been found so loaded that reproduction should cease. A poor stock is one which shows a number of cases of psychoses, mental defect and psychopathic states. A family history showing one or two cases is normal; all families have them

The falling birth-rate will soon lead to a decline in the total numbers of the population; a differential fall in the birth-rate has occurred so that those best endowed by heredity, intelligence

and personality have been producing relatively fewer children than the poorly endowed. *Positive eugenics aim at encouraging reproduction in the better stocks.* By family allowances, relief from taxation, and full educational opportunities for all, the economic barriers to large families should be greatly reduced. Spacing of births by contraception maintains the health of mother and children. Propaganda is needed so that people may develop a social conscience for the future of the human race. The positive measures can be applied to so many people that they are more hopeful than the negative measures applied only to a few.

The normal mental development of the child depends greatly on affection and security in the home. The child's personality is developed by the example and teaching of the parents. From them he should acquire emotional stability and correct standards of behaviour. Both parents are necessary to develop different aspects of the child's character. Their influence is difficult to replace. A broken home is one of the commonest of the predisposing causes of psychiatric states. Here are some examples of the percentages of homes broken before the patient's age of about 14 found in a wide variety of psychiatric states—39 per cent. of 4000 adolescent criminals (Norwood East, 1942); 17 per cent. of 155 manic-depressive cases, and 38 per cent. of 175 schizophrenic cases (Pollock, *et al*, 1939); 88 per cent. of 25 fugue states (Stengel, 1939 and 1941), and 31 per cent. of 87 war neurotics (Gillespie, 1942). Broken homes could, in some cases at least, be prevented by social measures. Where one or both parents have died, they have died relatively young, and some such deaths could be prevented. Separation and divorce of the parents might be less frequent if marriages were better planned. Illegitimate children frequently suffer from psychiatric states generally, and in particular, as Henderson (1942) has shown, from psychopathic states. He found that approximately 50 per cent of 34 illegitimate patients presented the picture of a psychopathic state. He quoted Binder's finding that of 350 mothers of illegitimate children only one-third were normal; one-sixth were feeble-minded and one-half were psychopathic. Less important causes of broken homes are prolonged sickness in hospital of a parent or of the patient; prolonged absence of the father at work involving living away from home or constant night-shift, the mother going out to work; and upbringing by grandparents.

If one adds to the homes broken by physical separation those "broken" by emotional instability of the parents or by dissen-

sion, then one may fairly claim that one or other variety is found in the great majority of all functional psychiatric states.

The housing conditions of the family have an important influence upon both mental and physical health. The Royal College of Physicians, London, has drawn up, at official request, a memorandum on the design of dwelling houses (*Brit. Med. Journ.*, 1943). The College makes practical recommendations for the general hygienic construction of houses and the simplification of the housewife's work; discusses the housing needs of special groups such as the aged, the tuberculous and the crippled. Special arrangements are needed for those anti-social tenants who do not care properly for their houses. All housing estates should be grouped round certain centres of public service, education and recreation.

Miserable surroundings must create misery of mind. Psychiatrists often obtain social workers' reports on the general home conditions including the state of the house. We frequently note some specific effects of bad housing—for example where overcrowding causes persons over 10 years of age to sleep in the same room as their parents or older siblings or other persons of the opposite sex. We are familiar with the harassed housewife who recovers from her symptoms after a few weeks in hospital away from it all (Gillespie, 1942). But one feels there is a good deal more in the relationship of bad housing conditions to psychiatric states which we should study and, in time, prevent.

Like housing, poverty is a subject which has been rather neglected psychiatrically We have not studied it very much. It has even been demonstrated (Neustatter, 1938) that children living in poor social circumstances show a smaller percentage of nervousness than children in better social circumstances. This illustrates again the danger of trying to attribute too much to social conditions. Nevertheless, we should know more about the psychiatric results of poverty One of the first security needs of the family is economic security. Yet it is a paradox of our present social system that the family creates poverty for itself. On a fixed income for the job, those with wives and children are the poorer. This is a convenient point at which to refer to the Beveridge Report, for Beveridge claims that the abolition of want was easily within the economic resources of this community before the war. Beveridge says that about three-quarters to five-sixths of all want is due to interruption or loss of earning power and practically the whole of the remainder is due to failure to relate income during

earning to the size of the family. He lists eight primary causes of need—unemployment, loss of livelihood by a person not formerly an employee, disease requiring treatment and rehabilitation, inability for work from disease or accident, childhood, marriage, retirement, and funeral expenses. I wish to emphasise the need for children's allowances. Beveridge recommends eight shillings per week for each child after the first, plus the existing provision in kind such as free milk—the allowances to continue as long as the child is in approved full-time education up to age 16. He recommends that the allowance be paid for the first child only when the responsible parent is in receipt of any benefit or pension under the Social Security Scheme.

It follows from what has been said about the family in general and about heredity and broken homes in particular that the adequate planning of marriages is of the greatest prophylactic importance in psychiatry. In addition, emotional difficulties between husband and wife are among the commonest problems with which the psychiatrist has to deal. Reform must begin in the home, where the children should have the example of their parents' happy and successful marriage. Parents to-day have often lost the respect and confidence of their children, and unfortunately do not get the chance of helping them with advice about marriage.

In the education of girls, domestic science and mothercraft should be much more developed. The advice of the physician should be sought on health and problems of heredity before marriage. Sexual difficulties in earlier life may hinder a person's adaptation to marriage. Parents seldom fulfil their duty of enlightening their children upon sexual matters. Needless worry over masturbation is a common cause of sexual maladjustment. Such worry is often the result of unduly repressive instruction by lay persons who have the care of young people.

Work

Work is man's biggest single activity. It should be one of his greatest joys, but often is not. Vernon's book (1940) on munition workers perhaps deals particularly with the balancing of maximum output with maximum health and efficiency in wartime, but most of it is applicable to peacetime workers too. Vernon describes how in the last war munition workers experienced so much sickness and loss of efficiency that in 1915 a Health of Munition

Workers' Committee was appointed by Mr. Lloyd George. The results were so valuable that the work was continued after the war by The Industrial Fatigue Research Board, known after 1929 as The Industrial Health Research Board. The Board is an official body and does not work for individual firms or train individual research workers. The National Institute of Industrial Psychology was founded in 1921 to meet these needs. Vernon correctly foresaw that the results of their scientific investigations would be neglected by many employers in this war, and he co-ordinated the investigations in this book. When unduly long hours are reduced, up to a point there is no reduction in the total daily output, and there may actually be an increase owing to improved efficiency. Adequate investigation will show what hours of work give the optimum output. The hours vary somewhat in different processes, and for men, women, youths and girls. One may say roughly that the weekly hours of work should not exceed 60 for men and 55 for women. Vernon recommends one full meal break only in each shift, but additional rest pauses in which refreshment may be supplied to the workers. He shows that night shifts for women are seldom necessary and that practically as good production can be obtained by having them work the two-shift system from 6 a.m. to 2 p.m and from 2 p.m. to 10 p.m. with a meal break of half an hour. One free day a week, usually Sunday, is necessary for both sexes. A few scattered days' holiday, plus one full week's holiday with pay, should be granted every year. So-called absenteeism is only partly voluntary, and much of it can be related to long hours of work or heavy work with fatigue and sickness. Only about one-fifth of all accidents are due to machinery moved by mechanical power. The remaining accidents are due to non-mechanical causes involving the human element. The frequency of accidents is influenced by the age and experience of the workers, fatigue, alcoholism, temperature and lighting. However, a few workers have significantly more accidents than the others, and it can be shown that they suffer from a definite condition of accident-proneness. Such workers are not always recognisable by aesthetokinetic tests, but if a worker employed in an occupation where accidents are liable to have serious consequences has more than one or two accidents, however small, within a limited time, he should be transferred to safer work. Health and efficiency depend also on correct ventilation, heating and lighting. Vernon points out the value of Safety Committees and of Welfare Work in industry.

Gillespie (1942) quotes some interesting observations on unemployment. After falling out of work there is a short period of a sense of release (a holiday freedom); gradually anxiety and depression set in with *loss of mental equilibrium*; *finally, after* several years, adaptation takes place to a new and debased level of life, lacking hope as well as fear of the future. Unemployment of the father appears to have a specially harmful effect on the child. Unemployment renders the father ineffective from economic, social, and possibly disciplinary points of view.

Coal and shale miners are one group of workers in whom I have been particularly interested. Mining is a dangerous occupation. The accident rate among miners is three times as great as among workers in other industries. Also, while men in the insured population as a whole are incapacitated by sickness for an average of 8·7 days a year, in miners the corresponding period is 18 days (*Lancet*, 1941). The problem may be to some extent a psychiatric one People are apt to think that because mining is a dangerous occupation, *therefore miners can not be nervous.* This is not so. We see many nervous miners at the Jordanburn Nerve Hospital. It is surprising how many of them suffer from fear of the job, from worry about the job, from anxious dreams about the job, and give dramatic accounts of accidents in which they have been involved or which they have witnessed I do not of course think that danger at work is the sole cause of their illnesses. Persons predisposed to nervous illness should be excluded from mining. Many social measures can be taken, and are now being officially taken, to promote the industrial health of miners. These include the provision of canteens and of pit-head baths, the increase of the official medical officers of the Ministry of Fuel and Power from one to ten, improvement of first-aid and ambulance organisations at the pits, prevention of miners' occupational diseases, payment of the expenses of a miner sent by his doctor for out-patient treatment, and the setting up of a rehabilitation centre for miners in Scotland (*Lancet*, 1942).

Accidents, Diseases and Rehabilitation

Accidents are of three main groups—road accidents, industrial accidents, and those occurring in private life, especially at games or in the home. The figures are very large In 1938, 6648 people were killed and over 226,000 injured in road accidents (*Brit. Med. Journ.*, 1939). In the same year, industrial accidents caused 944

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deaths and just over 179,000 injuries involving more than 3 days' absence from work (Chief Inspector of Factories, 1939). About 8000 people die every year from accidents in private life. The causes of accidents are innumerable, but accident-proneness causes a number of road and private accidents as well as industrial ones. Other social factors can be demonstrated: the Royal Society for the Prevention of Accidents (*Lancet*, 1943*a*) has analysed 1153 fatal accidents of private life, and the figures show that many can be related to definite causes. Thus 80 per cent. of the scalds were received by children under four who had been left near teapots and kettles, and had pulled them over on themselves. Of the 142 deaths from burns, 44 were of children playing near unguarded fires or lighted candles, or left alone in the house. Apart from children, old people are common victims of accidents; thus 395 of the 582 victims of falls were over the age of 65.

Accidents may occasionally be the direct causes of organic psychiatric states. Much more often they are the indirect or precipitating causes of functional reactions. Such cases can be very difficult, especially industrial or traffic cases where compensation and litigation are involved. It is only occasionally that a psychiatric state follows an accident in which the patient was not injured at all or which he merely witnessed. The patient has usually himself suffered an injury although it may not be very severe—for example, extensive bruising, a simple fracture, or a transitory concussion. Nevertheless, no matter how long after the injury the psychiatrist sees the patient, it is not easy to convince him that his symptoms have changed from organic to functional. Another form of treatment—rehabilitation—is required, and it should be applied at a very early stage. Modern rehabilitation programmes have, as one of their main objects, the maintenance of a good morale among injured persons. Many post-traumatic neuroses might be prevented by general rehabilitation—not *necessarily specially psychiatric in its bias.* When necessary, psychiatric treatment could be combined with rehabilitation.

So far as disability due to traumatic neuroses is concerned I wish to point out a possible danger in the Beveridge Report. Whereas one of Beveridge's main principles is that as many types of benefit as possible are to be at one flat subsistence rate he does propose specially generous treatment for disability due to industrial accident or disease. This may be desirable in organic cases, but it would be demoralising for the post-traumatic neuroses, and I think that all who are familiar with the so-called

"compensation neuroses" will agree with this. It is difficult to say what should be done because such neuroses are in fact precipitated by industrial accident and injury. Perhaps in these cases a time-limit for the high industrial benefits might be automatically imposed.

Like accidents, almost any type of bodily disease may be a direct organic or an indirect emotional cause of psychiatric states and, as a parallel to accident proneness, psychiatric states may be a cause of bodily disease. Some bodily conditions are of special interest in social psychiatry.

Infections and epidemic diseases should be socially preventable diseases, but we can point to many chronic victims of epidemic encephalitis and to some victims of brain damage complicating the infectious fevers of childhood.

Venereal diseases are the direct causes of such conditions as general paralysis, but they have other psychiatric aspects. Fear of venereal diseases and guilt about having contracted them are not uncommon psychiatric symptoms. I do not think, however, that propaganda has any appreciable harmful effect in increasing these feelings. The incidence of venereal diseases is related to social conditions, as shown by the increase which has occurred since the war. Among patients suffering from venereal disease are some of the social problem group previously mentioned—people who refuse treatment for themselves and spread the diseases to others. Defence Regulation 33b offers a measure of control.

Nutritional diseases are amongst the most characteristically social of all diseases. In other countries pellagra causes many serious psychotic conditions, but such conditions, due primarily to faulty diet, are extremely rare here. It has been suggested recently that deficiency of the water-soluble vitamins, and especially of vitamins of the B group, is important in certain apparently neurotic syndromes, in some acute deliria after operations and delivery (Sydenstricker, 1943) and even in senile dementia (Stephenson, *et al.*, 1941).

The so-called *psychosomatic diseases* include bronchial asthma, peptic ulcer, ulcerative colitis, hyperthyroidism, migraine, essential hypertension, postural defects including visceroptosis, and some skin diseases It is being increasingly recognised that these diseases develop in people with certain types of personality, especially the anxious personality. In the course of life, as such persons react more intensely than others to their duties and responsibilities, they may develop one of these diseases. The

present view is, generally speaking, that one can recognise these particular types of personality, but just how the illness is produced is a mystery. The psychiatrist makes no claim to be able to cure the psychosomatic diseases by his methods alone. It is probable that a double approach, from both the emotional and the physical aspects, will always be needed in these conditions.

Any bodily condition about which a person is sensitive, or which makes him feel different from others, may cause much *feeling of inferiority, especially if the condition is chronic or* permanent. There are a great many such conditions. Some important examples are skin diseases on exposed parts, squint in children and deformities of the genitalia. Adler used the term "organ inferiority" to describe such conditions, and gave it almost primary importance in his psychopathological theories.

Having discussed accidents and diseases, we may now discuss rehabilitation therefrom. Rehabilitation has recently been greatly developed from both the surgical and the medical aspects. The Beveridge Report emphasises the need for it, especially if disability benefit is to be paid at the full rate as long as the disability persists. The Tomlinson Report (1943)—or Report of the Inter-departmental Committee on the Rehabilitation and Resettlement of Disabled Persons—discusses a comprehensive scheme. The report states that complete rehabilitation and resettlement are more difficult in medical than in surgical disablements. The best form of resettlement for a disabled person is employment which he can keep on his merits in competition with his fellows. This is possible much more frequently than is generally believed. Disablements due to neuroses and psychoses are discussed. Many neurotics will be able to return directly to ordinary employment. A minority remain as problem cases and misfits, and neurosis is being increasingly recognised as a cause of wastage and absenteeism. The Committee do not actually say, but they appear to imply, what I think is the correct view, that the resettlement of psychiatric cases is a very individual problem which cannot be dealt with by rule of thumb methods and about which we need to learn a great deal more. Rehabilitation generally should be under even closer medical control than is envisaged in the Tomlinson report (*Lancet*, 1943*b*)

Specific Psychiatric Conditions

In almost every type of psychiatric case, social factors play a greater or lesser part; they are seldom entirely lacking. There

are, however, some specific types where social factors are perhaps particularly important either as causes or as offering opportunities for preventive or remedial action.

Alcoholism (Henderson, 1937*a* and 1939) is usually the result of a psychopathic personality and the life history of that personality. In the setting of such a personality alcohol, even in small amounts, may lead to serious social effects such as murder, assault and sexual offences, and to suicidal attempts. Alcoholism in the parents has a prejudicial effect on the children, principally from its disruptive influence in the home. Alcoholism can be the direct cause of mental illnesses such as delirium tremens and Korsakow's psychosis. The incidence of alcoholism can be reduced by social measures such as increased taxation of alcoholic beverages, restriction of hours of sale, reduced number of licences, local option, better facilities for the recreation and amusement of the public, and above all, education and propaganda to develop social conscience in this matter. In fact, the incidence of alcoholism is now very much less than it used to be.

The incidence of *juvenile delinquency* is much greater than it was, having been rising for some time. It was only after 1933, the year in which the Children and Young Persons Act was passed in England, that the increase in the figures began to assume serious proportions (Carr-Saunders, *et al.*, 1942). It may be that the better provision made for young offenders by this Act led to more cases being brought before the Juvenile Courts, and that the real increase is not so great as might appear. Juvenile delinquency is often a psychiatric problem. Personal and social causes can be recognised in many cases. The public are sometimes alarmed when the psychiatrist makes this claim and think that he wishes to supplant Juvenile Courts by out-patient clinics. This is not so; it is co-operation that is required. Psychiatrists should be appointed to the Juvenile Courts to advise in the disposal and treatment of the children. The facilities and organisations at the command of the Juvenile Courts are fully appreciated by the psychiatrist, who seeks to extend, not to displace them. It is true that at present psychiatric treatment usually means out-patient treatment. Then the children are not controlled, relapses are frequent in the early stages, and psychiatric treatment falls into disrepute. The psychiatrist himself knows full well how much supervision and control juvenile delinquents need, and what a high proportion of readjustments are effected by prolonged re-education in Voluntary Homes and

Approved Schools. Detailed psychiatric investigation often leads to a more serious view being taken of the case than before and the more delinquents are examined psychiatrically the greater—not less—will be the demand for treatment in such institutions. But at present committal to such an institution often means the end of psychiatric treatment, as the clinic may be far away. There is great need for special residential accommodation which will combine the benefits of the present lay re-education with psychiatric supervision and treatment. This should be supplied officially, while out-patient treatment should be supplied voluntarily until we are surer of our methods there.

The same applies to *older criminals*. Norwood East and Hubert (1939) warn against too much reliance on out-patient treatment, and suggest the creation, within the present prison system, of a special penal institution for the investigation and treatment of specially selected cases. Such an institution would deal with quite different cases from those already treated in criminal asylums.

Suicide (Henderson, 1937*b* and 1938) is, like alcoholism, much determined by internal causes. Yet important social factors can be recognised. The suicide rate has been increasing steadily since the beginning of the last century. In Scotland the suicide rate was almost doubled between 1921 and 1931. Suicide was less common in the past when the Church and the Law had more controlling power; it is still less common in the predominantly Catholic countries than in the predominantly Protestant countries. It is more common in spring and early summer than at other seasons. It is much more common in certain occupational classes than in others. The type of suicide at least is influenced by the means available; for example, the use of poisons and firearms is decreased by appropriate legislation. One unusual type of suicide, reported by the newspapers, may be repeated by other patients elsewhere.

In *schizophrenia* there is usually a history of prolonged social maladaptation more severe than in any other psychiatric state. The previous personality has been well described as "shut-in," and throughout the patient's life his withdrawal from the environment and his introspection increase till they culminate in the psychosis. It has been demonstrated statistically that the social life of the parents is singularly restricted during the childhood of many of the patients (Pollock, *et al*, 1939) which may be important in initiating the patients' failures in social activity; and that those

patients who had adequate reactions to work, social life and sex have a better prognosis than those who had inadequate reactions (Stalker, 1939). In the etiology of schizophrenia there is much that is constitutional or unknown, but one sometimes finds patients who have passed through an extreme form of the usual adolescent speculation upon the nature and meaning of the world. They have had severe conflicts about religious, philosophical, political, scientific and sexual matters. These conflicts can sometimes be traced into the psychosis. It is often patients who have suffered in this way who make a good recovery (Kasanin, 1933).

In *involutional melancholia* social factors are much more important than has been generally realised. The previous personality in involutional melancholia has only been recently described (Titley, 1936; Palmer and Sherman, 1938). This personality is rigid, over-conscientious, over-moral and over-religious. Social interests are limited. Life is guided by a fixed routine; the patient lives in a rut; his work is often of a subordinate type and he fears responsibility. The need to follow a fixed pattern throughout the years is the principal feature, and in it lies the danger. If anything happens at the involutional period of life to alter the pattern, the patients may be unable to adjust to it. These happenings are what Palmer and Sherman call "threats to the integrity of the ego" or what one may call "uprooting" factors. Over and over again one finds that involutional melancholia is precipitated by a social change which radically alters the patient's way of life:—the employee who through no fault of his own loses the job he has had for 30 years; equally important the employee who for his good record is promoted to a position of responsibility which he cannot tolerate; the business man who becomes bankrupt; the man who retires and has had no interests besides his work; the elderly spinster who has stayed at home to care for her parents and finds herself lost when they die; the mother who finds all her children have now married and left her; the spouse who loses the marital partner by death—when such things happen at the involutional period to people with these rigid personalities melancholia may be precipitated.

In conclusion, I wish to offer two explanations—almost apologies. Firstly, in trying to discuss social psychiatry generally I have dealt with the various subjects briefly and perhaps too dogmatically. Secondly, I have discussed subjects which you may say are not specifically psychiatric. I agree, but say that

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psychiatry has something to offer in these subjects, and that in return psychiatry has a great deal to gain from the help of those working in other branches of medicine.

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DELINQUENCY

By DOUGLAS KERR

In the last few years much attention has been drawn to *delinquency, the responsibility of delinquents, their treatment* and possible cure; especially in regard to juvenile delinquency and its rapid increase. Many overstatements have been made, and the problem and the rôle of medicine are not generally appreciated. One of the post-war social movements will have to be a determined attempt to tackle this problem. It is a problem in which we as a community are all interested. As medical men we have a further interest. I have been impressed in the past with the very great help some practitioners have afforded their patients who have fallen from grace, and, on the other hand, with the lack of appreciation of the situation by others. By many, delinquency would be considered outside the sphere of the general practitioner and to be a matter for a psychiatrist or psychologist; but in so many instances the solution is not a cure by medical means but an adjustment of the home surroundings, which a practitioner who is well acquainted with the home and his patient's character may perhaps be best qualified to advise. At other times the practitioner's appreciation of the underlying causes of minor delinquency which do not actually result in an appearance in Court, such as juvenile delinquency, sexual offences, some cases of shop-lifting, drunkenness, etc., may be the means of providing the patient with skilled advice.

Improvement in social conditions is one of the fundamental principles in preventative medicine. It is also of prime importance in the problem of delinquency. So much has been said recently about the scientific treatment of delinquency that we are apt to forget the part played by social conditions, and there is a tendency to try and explain all anti-social conduct as being due to abnormal mental complexes. It seemed to me that it would be of value to survey the question of delinquency, so that we might appreciate the relative parts played by medical as contrasted with social conditions in its causation; and also that, whilst in justice to the individual mental abnormalities must be taken into account

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when dealing with a delinquent, the interests of the community must also be considered.

It is characteristic of a new method that its enthusiastic supporters overstate the case. This is so with delinquency. There are some people who have so lost their sense of proportion that they would have us believe that all delinquency, especially juvenile delinquency, indicates mental abnormality and requires psychological treatment rather than punishment.

I have heard a well-known psychiatrist argue—the accused has committed a murder, therefore he must be insane! The question remains, How am I to prove he is insane? We can all think of instances which disprove such a contention.

It cannot be too strongly urged that delinquency is not of itself evidence of disease or of an abnormal mental condition. The great majority of delinquents are not suffering from mental disease or mental abnormality. There is, however, a small proportion who are mentally ill or abnormal, either quite irresponsible or whose responsibility is diminished. It is in these that we are particularly interested It is as well, however, that we should realise that they are only a small percentage of all delinquents. We shall then be able to assess the rôle of medicine in the prevention and cure of delinquency in its true perspective.

I propose first to deal with the ascertainment and disposal of abnormal mental delinquents appearing before a Summary Court, and in general to follow the routine in the Edinburgh Burgh Court, as this exemplifies some of my conclusions and explains how abnormal delinquents are detected and their percentage estimated.

Many persons only appear before a Court after the delinquency, or perhaps abnormal conduct better describes the offence in a number of instances, has been going on for some time. Sometimes the family doctor has been consulted, and in a considerable number of cases he can often do all that the Court does in an attempt, frequently with success, to end the delinquency.

The type of case naturally varies considerably; for instance, a naked man walked into a tobacconist's shop early one morning and asked for cigarettes; any layman would realise the need for medical attention. Not so evident is the case of a man who disarmed the sentry at Holyrood Palace. This might have been the result of a bet or a drunken spree, but when it emerged that he did so as he wanted to carry off the statue of Edward VII, he was referred for medical examination. Another example is

that of a man who threw a stone through a shop window. He was charged with malicious mischief, and gave as his explanation that he did not know why he did it, but that he was fed up. He was perfectly sober and to the police appeared quite normal; on examination his condition became evident and he was sent to an asylum Had he appeared before a Summary Court, where there was no routine system of examination, he would have been sent to prison I mention this case as the offence is one which most people would not perhaps associate particularly with mental abnormality. It is, however, a frequent offence, and the delinquent is often mentally abnormal. The last instance of this offence with which I came in contact was only a week or two ago, when a patient threw a stone through his doctor's dining-room window. In this instance, however, the patient was perfectly sane. Finally, let me take the most common offence of all—drunkenness; the common "drunk" that appears before the Court. A woman charged with being drunk came under my observation. She had two recent previous convictions for drunkenness, but had had no convictions before that. Being unable to pay a fine on her first conviction, she had spent some days in prison On examination she was so depressed as to be mentally abnormal. As her history was investigated she was found to be looking after the illegitimate son of her daughter who was out at work all day. Instead of helping her, her husband and the neighbours on the stair all cast up her time in prison and the illegitimacy of the child. She had no one to turn to for sympathy, became very depressed and commenced to drink. She was at the beginning of the career of an habitual drunkard. The cause of her depression and delinquency having been ascertained, she was admonished and put into touch with the social services attached to the Court and though several years have now passed she has had no other appearance before the Court.

One could multiply examples without end; but I selected these four cases, as the first is clearly a case which would strike a lay magistrate as requiring medical examination, the second is not quite so obvious, and the last two are such common offences and would in most Courts have passed undetected and been sent to prison

It is evident that the first problem which we have to overcome is detection of the mentally abnormal, as in many instances the condition is not obvious, and even certifiable insanity may pass unnoticed.

The usual manner in which the problem is dealt with in most Courts is that if the Magistrate, or in the Sheriff Court the Sheriff or Procurator-Fiscal, has evidence which suggests that there is a mental element present, a medical report may be obtained. It will be clear that these delinquents are those whose condition is such that it suggests to a layman that they are abnormal, and that many other abnormal delinquents will pass undetected.

The only other way in which we can deal with the problem is by some system of routine examination. This perhaps accounts for the suggestion that all delinquents, especially juvenile delinquents, should be psychologically examined.

Now it is quite possible, and even desirable, that every delinquent admitted to a prison for more than a few days' sentence should have a preliminary investigation to ascertain whether further mental examination is required, a procedure which, I am afraid, is not carried out in Scotland. It is, however, quite out of the question, and it is also unnecessary, to examine every delinquent appearing before a Summary Court.

There are, however, certain classes of individuals, and particular offences, which are so often associated with mental abnormality that they call for a preliminary investigation from that aspect. You will note that I say preliminary investigation. It is, of course, out of the question to investigate a difficult case thoroughly at a Police Court; but an interview with the friends or relatives and a preliminary examination will show the need for further investigation in difficult cases, which is the main purpose of the examination. Such difficult cases are few. In the majority of instances the preliminary examination gives sufficient information to enable the delinquent to be dealt with in the most suitable manner.

This procedure results in selected cases being automatically marked for medical examination. There is already the beginning of this system in the Departmental Committee's recommendation in regard to sexual offences against children, that all offenders should automatically be referred for mental examination before sentence.

Some of the less obvious offences which suggest the desirability of a medical examination are:

(*a*) Malicious mischief

(*b*) Arson.

(*c*) Impulsive conduct for which the accused is unable to give a reason.
(*d*) Shop-lifting in the case of the aged or at the menopause.
(*e*) Petty thefts by hitherto respectable persons in good positions.
(*f*) Assaults.

1. If unprovoked, especially of a stranger.
2. Wife assaults when the husband alleges wife is unfaithful but has never managed to prove it.
3. Bogus assaults.

(*g*) Frequently following or molesting a particular person of the opposite sex.
(*h*) Running away from home (adolescents).
(*i*) Sending obscene anonymous letters.
(*k*) All sexual offences (except prostitution).

Now it may be said that with any such system of routine examination, many abnormal delinquents will pass undetected Whilst this may happen occasionally, I do not think it is a frequent occurrence.

In this connection it is interesting to note the geographical situation of Edinburgh. Unlike most large towns in England, which may be almost continuous with or only a few miles distant from other large centres of population, Edinburgh is shut off from any other populous area. It lies at the centre of a circle, the upper half of which is shut off by the Firth of Forth, and the lower semicircle is fringed by the Moorfoot, Lammermuir and Pentland Hills and moors; sparsely populated areas extending for a depth of twenty miles or more. The nearest town is Glasgow, fifty miles away. This tends to keep the Edinburgh delinquent, especially the minor delinquent, in Edinburgh. Again, the City of Edinburgh has only one Police Court through which all delinquents pass, with very few exceptions, however serious their offence. They are either dealt with there or remitted to a higher Court. The result is that if abnormal mental conditions are causing an individual to commit delinquencies, and his condition passes undetected, he will appear again and again before the same Court, until his frequent appearances attract attention, and his condition is recognised.

The same applies to the disposal or treatment of delinquents recognised to be abnormal If this is unsatisfactory, the delinquent

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to do so is an indictable misdemeanour. Even at the present time people are sent to prison in England for this offence, with the idea that rest, good food and quiet, perhaps in the prison hospital, enables them to gain an even emotional level In Scotland, to commit suicide or to attempt to do so is no offence, provided the individual does not alarm the lieges, in which case he will be arrested for committing a breach of the peace. Such a charge is usually made so as to ensure that the individual is properly looked after and his future well-being arranged for by his relatives, or by his being brought into touch with the social services attached to the Court. I recall one case where such a charge could not be made: a man walked up to a policeman on point duty and quietly asked him if he would send for an ambulance, as he had drunk a bottle of lysol. The policeman was not alarmed and proceeded to telephone for an ambulance. The man was taken to hospital. No breach of peace took place, and no charge could be made. In Edinburgh many such cases never appear before the Court, suitable and adequate arrangements for their future being made by their relatives.

I can quite understand the desirability of retaining attempted suicide as a misdemeanour in England, as in many instances the quickest and surest method of placing the individual under restraint is to arrest him; but to sentence him to prison, even at his own request, can hardly be defended. Surely a prison, even a prison hospital, is not the environment conducive to the recovery of a person suffering from melancholia or depression, or from a feeling of unworthiness or inferiority. I have never met an attempted suicide who wanted to go to prison If a person requires institutional treatment he should be admitted to a mental hospital If he is not certifiable and refuses to enter a mental home of his own accord, he can safely be allowed to go home, preferably in charge of his relatives. It so happens that all successful suicides in Edinburgh are reported to me as the Police Surgeon. Though I have seen many suicides who have previously been admitted to a mental hospital after an attempt at suicide, I cannot recall any suicide, though no doubt there were some, who had previously been charged with attempted suicide and who, after examination, had been discharged without institutional treatment. In my experience the act of attempting suicide often serves as a safety valve, and as soon as the immediate physical effects are recovered from, the individual has in many instances regained his mental equilibrium I can see no justification or

will again appear before the Court if his mental condition is the cause of his delinquency. If there is no reappearance, then the arrangements made by the Court or the sentence imposed has, presumably, had the effect of ending the delinquency. It is important to realise that because an individual is mentally diseased or abnormal, it does not mean that he is unsuitable for punishment or that punishment will not have a deterrent effect. Many mentally abnormal and even certifiable individuals know quite well that the particular offence with which they are charged is wrong, and in certain circumstances are deterred by punishment All asylums have a system of punishments by deprivation of special privileges, and many of the inmates are deterred from wrong-doing by fear of losing some of these privileges There are also many border-line psychopaths whose condition would be aggravated, and their delinquencies multiplied, if it were suggested that they were not responsible, and could offend with impunity.

In Scotland the Law recognises a condition of diminished responsibility; that is to say, some aberration or weakness of mind, a state bordering on insanity although not reaching it, a mind affected so that responsibility is diminished from full to partial responsibility. Such a condition of mind, whilst not excusing the offence, may reduce its seriousness and call for a lesser punishment. Where such diminished responsibility exists, the delinquent must be given medical treatment or receive punishment, or both. In the interests of the community he cannot be allowed to repeat his offence at will and escape punishment or segregation, and frequently punishment has a deterrent effect.

In general, the severity of sentences is becoming less. The modern outlook of a Court should be, not punishment merely because an offence has been committed—though to some extent this may be necessary as a deterrent to others—but, especially in Summary Courts, adjustment and arrangement so that the individual may be able to take his place in the community. In this adjustment punishment may find a place; but in many minor offences, and even in serious cases under certain circumstances, the end can be better achieved by admonition or probation, though this in turn can be overdone.

Not only do the abnormal delinquents vary from those certifiably insane to those described by their relatives as "highly strung," but the method of dealing with them varies in different places. In England, to commit suicide is a felony, and to attempt

to do so is an indictable misdemeanour. Even at the present time people are sent to prison in England for this offence, with the idea that rest, good food and quiet, perhaps in the prison hospital, enables them to gain an even emotional level. In Scotland, to commit suicide or to attempt to do so is no offence, provided the individual does not alarm the lieges, in which case he will be arrested for committing a breach of the peace. Such a charge is usually made so as to ensure that the individual is properly looked after and his future well-being arranged for by his relatives, or by his being brought into touch with the social services attached to the Court. I recall one case where such a charge could not be made: a man walked up to a policeman on point duty and quietly asked him if he would send for an ambulance, as he had drunk a bottle of lysol. The policeman was not alarmed and proceeded to telephone for an ambulance. The man was taken to hospital. No breach of peace took place, and no charge could be made. In Edinburgh many such cases never appear before the Court, suitable and adequate arrangements for their future being made by their relatives.

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necessity for sentencing a man charged with attempted suicide to a term of imprisonment.

I have referred to attempted suicide, an act which, except in a few instances, is due to mental causes, as illustrating the divergent views on the manner in which abnormal delinquents should be dealt with. There is, however, a growing tendency, whenever there is a suggestion of mental abnormality, to obtain medical advice. In the lesser Courts especially, cases are being referred for examination and treatment to psychological clinics. This is, of course, all to the good. Excellent results or complete cures may follow treatment, especially in sexual offences, as well as in some other conditions. If we are to view the results in their proper perspective, however, we must realise that excessive claims are made by many advocates of this procedure. Some clinics claim a high percentage of cures of delinquents sent for investigation and treatment. The criterion of cure in one well-known clinic—not in this city—is no Court appearance for six months after treatment has finished. With such a criterion I think most Courts could claim to have cured many habitual drunkards or mild maniacs with a small fine.

Medical investigation and care have a definite place in the treatment of delinquency, but we should appreciate that it is only in relatively few instances that we can cure delinquency by medical means. Most gratifying results can sometimes be obtained, but the main value of medical investigation is the ascertainment of the mental condition. This ensures that any abnormality is taken into account, and in many instances may contribute, especially in the lesser Courts, to the prevention of further delinquency by bringing the individual into contact with the social services attached to the Court. That is to say, in some cases the patient may be altered to fit his surroundings, but in many instances the surroundings, environment, or occupation are adjusted to enable the delinquent to carry on in the community without friction or further behaviour troubles, except of a minor nature. Every effort should be made to see that an abnormal offender who will benefit by treatment obtains such treatment, or if treatment will not remedy the condition, such for instance as in the case of a high grade defective, that other measures are adopted. There are, however, a number of delinquents whose mental abnormality is recognised but is not such that they can be certified, and who refuse to co-operate. They become chronic offenders and appear time after time before the Court.

The first and foremost problem from the medical aspect is detection of the mentally abnormal delinquent, and I have indicated how this can be done. In considering this, one is apt to magnify this aspect of delinquency to the exclusion of others. We must therefore consider what proportion of mentally abnormal delinquents may be anticipated.

Dr East, Medical Inspector of H.M. Prisons, and formerly Senior Medical Officer of Brixton Prison, has given figures based on nearly 15,000 remand prisoners in Brixton Prison; of these, 1·5 per cent. were insane, 1·3 per cent. certifiable under the Mental Deficiency Acts, and 1·4 per cent. showed uncertifiable but abnormal mental conditions. A total of 4·2 per cent. of the whole. These were prisoners on remand, and in 10 per cent. of cases a report was called for by the Court as to their mental condition. It is therefore safe to assume that part of the total were a selected group of suspected abnormally mental delinquents who, but for their mental condition, would not have been remanded to prison. Allowing for this, these figures correspond approximately with my own experience.

Any figures I can give you can *only* be approximate, as it is difficult to estimate accurately the total number of individuals appearing before a Summary Court who can be considered delinquents as contrasted with offenders against bye-laws. Simple drunkenness, which supplies a large part of the annual total of offences, should also be excluded. In the four years prior to the war, of those offenders charged with dishonesty, violence, breach of peace, sexual offences and similar delinquencies—that is to say, excluding drunkenness, offences against bye-laws and the Road Traffic Act—1·4 per cent. were admitted to mental institutions, either as insane or defective. The actual percentage of certifiable cases is higher than this, as many found to be certifiable but harmless are taken care of by their relatives, or if defective may be boarded out by the Public Assistance Department; 1·5 per cent. showed mental abnormality, which contributed to or was the cause of their delinquency, but was not certifiable, and 0·6 per cent. showed slight abnormality unconnected with their delinquency: a total of 3·5 per cent. That is to say, that leaving a margin for undetected cases and for any error in the total number of delinquents, approximately 96 per cent. of delinquents are mentally normal individuals.

From these figures it will be evident that as far as adult delinquents are concerned, the statements made by some people

that delinquents should not be treated as offenders but as patients requiring medical attention, cannot be supported. Whilst to any one delinquent it may be of paramount importance, medical science can only play a small part in the whole problem of adult delinquency. Can it be said that it plays any greater part in juvenile delinquency?

It is perhaps in this class of delinquency that the most exaggerated claims have been made, and suggestions have been put forward by laymen that all juvenile delinquents should be examined at a psychological clinic. The problem here is very different to that of the adult delinquent. The offenders are at school, or have only recently left, and considerable information about them is available. Before appearing in Court, the case is notified to the Education Authorities, who furnish a statement of various particulars from their record concerning the child and its parents. If the Education Department of the area is satisfactory, any mental defect or subnormality should have been detected at school and its degree reported upon; an important point, as if the child is mentally abnormal, the abnormality, except in very few instances, is the degree of mental defectiveness or subnormality. The information from the Education Authority is forwarded to the Juvenile Organisations' Committee of the area some days before the child is due to appear in Court. A Probation Officer learns at first hand particulars about the child, visits the home, and is present in Court when the child appears. If there is anything which suggests to the Probation Officer the desirability of a mental examination, this is carried out, but in most cases this is not required. Apart from subnormality and mental defect, which should indicate themselves from the school records, juvenile delinquents requiring psychological examination and treatment are a fraction of 1 per cent We should perhaps keep in mind, in this connection, that we are referring to delinquents and not to difficult or problem children at school; in these latter, especially in girls, psychological treatment may frequently be of advantage.

What is wanted in regard to the growing numbers of juvenile delinquents is not the establishment of psychological clinics, but the provision of adequately trained Probation Officers. Much of the work done at a psychological clinic would be better done by competent Probation Officers The real value of a clinic is that it is in the background to supplement the Probation Officer when necessary, either in the examination of the child or in

questioning the parents. Some parents would quite willingly fall in with a doctor's advice when they would resent the questions of a Probation Officer.

The great majority of juvenile delinquents are mentally normal, and it is neither necessary nor desirable for a Court to send large numbers of juveniles to a psychological clinic. Indeed, it is not too much to say that such a procedure may do definite harm to the children concerned.

To sum up the position, we see that approximately 96 per cent of delinquents must be considered mentally normal individuals. We must therefore disabuse ourselves of the idea that by the scientific medical treatment of delinquency we are going to materially alter the situation. If every mentally abnormal delinquent was eliminated it would only scratch the surface of the problem The position in regard to juvenile delinquency is much the same, and here we must be careful that by injudicious medical intervention we do not do more harm than good. At the same time, we see that for the individual delinquent the ascertainment of his condition may be all-important; that there should be some means which would ensure ascertainment of the mentally abnormal; and that examination of the delinquent should not be left until the mental abnormality is so great that it can be detected by a layman.

The object of this address was to indicate the rôle of medicine in relation to delinquency in its true perspective. Time does not permit of a detailed survey of the whole question of delinquency, but it is only fitting that I should indicate briefly the main problems.

It is true that individuals from a psychopathic stock may be of such a make-up that, when subjected to certain strains, they are not able to resist temptation or they react in a manner that produces delinquencies, and that they may therefore inherit a potentiality for delinquency; but something more than their inherited make-up is necessary to produce delinquency, some precipitating factor.

Investigations into delinquency and its causes have all pointed to social conditions and environment as being the main causal factors. An enquiry by Edinburgh Corporation into the causes of juvenile delinquency showed the causes to be social conditions, environment and lack of parental control and training Many of these juveniles have now grown up, and the widespread dishonesty and lack of appreciation of right and wrong in these

young people, so frequently commented upon by judges at the present time, is an indication of the results. Their children in turn will grow up under the same environment and lack of parental example and training, and so the vicious circle will go on. I am a great believer in probation, and have many times recommended probation for serious offences, in suitable cases; but by the almost automatic sentence of probation on all juvenile offenders, the Courts are at present manufacturing criminals. Last year in Edinburgh there was a marked fall in juvenile delinquency, which the Chief Constable attributes to the severer measures taken with offenders. Whilst this will no doubt contribute to a considerable extent, the main problem is a sociological one—an improvement in social conditions and the training of the young, both at home and *at school*, in a sense of discipline and in a respect for the law, so that they may grow up with a sense of right and wrong and in turn bring up their children in the way they should go.

SOME RECENT ADVANCES IN CHEMOTHERAPY

By WILLIAM O KERMACK, M.A., D.Sc., LL.D.

From The Laboratory of the Royal College of Physicians

FROM its derivation, the word "chemotherapy" might well mean the application of chemistry to the cure and treatment of disease. In this broad sense of the word it would, I imagine, be admitted that chemotherapy covers a very large proportion of the whole field of modern medicine. Apart from the application of chemical analysis in the study and diagnosis of disease, the control of food and water, and in the public health services generally, recent advances in the field of hormones and vitamins, advances of the greatest importance for curative and preventive medicine, have depended in large measure on the work of organic chemists in isolating, identifying, and synthesising active compounds. The whole activity of the body depends on the chemical processes going on in its cells, and so, as medical knowledge becomes more scientific, it necessarily becomes more chemical in its basis.

But it is not with this wide meaning that the word chemotherapy is used to-day. The modern science of chemotherapy owes its conception and birth to that great genius and benefactor of mankind, Paul Ehrlich Following up the pioneering work of Pasteur, he had developed the theory and practice of immunotherapy. This new science had achieved great successes in dealing with diseases due to viruses, as we should now call them, and to bacteria But against protozoal infections the new methods were singularly unsuccessful. Stimulated, no doubt, by the long-known therapeutic effects of quinine in malaria and mercury in syphilis, he conceived the idea of modifying his methods in the sense of replacing the naturally produced immunological weapons by pure chemical compounds, highly toxic to the parasites but relatively innocuous to the cells of the host. The problem was to discover the chemical compounds with the desirable properties, and for this purpose Ehrlich made use of the notions and the experimental technique he had already developed in his immunological researches.

We shall, then, take the word chemotherapy as designating

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the application of well-defined chemical compounds for the purpose of ridding the animal organism of pathogenic parasites. This definition, you will notice, contains certain elements of vagueness; but any definition of a science is likely to be somewhat vague, for the boundaries of a science are usually indefinite and arbitrary, like the boundary between the North Sea and the Atlantic Ocean. Who, for instance, can say just where physics merges into chemistry, or where physiology ends and psychology begins?

I have spoken of a "well-defined" compound. The chemist prefers, if possible, to deal with pure substances of known constitution, and in modern chemotherapy most of the compounds experimented with belong to this class; but it seems desirable to leave the definition sufficiently elastic to include such substances as emetine, though its constitution is not known with complete certainty, and even such substances as Fleming's penicillin, which though not yet completely characterised chemically, is yet unambiguously defined by its method of production (see p. 281). On the other hand, vague extracts of plant and animal tissue where any action observed might be attributed to any one of a dozen constituents, are best excluded from our field, for we do not wish to encroach on the preserves of the wise-wives, the witch-doctors and the herbalists.

Another word in the definition calls for a remark. By parasites we mean living organisms dwelling in, or on the surface of, the body. Usually it is with micro-organisms that we are most concerned, but the boundary is again an indefinite one, and it is convenient to include, for example, anthelmintics amongst chemotherapeutic agents. There are other obvious difficulties; we would certainly include within chemotherapy the use of sulphonamides to sterilise wounds or prevent the infection of burns, but whether it properly includes de-lousing or de-fleaing agents is a more doubtful question, to which most of us would probably give a negative answer.

Be this as it may, it will be seen that the subject of chemotherapy covers only a small fraction of the applications of chemistry to curative medicine. Even so, the field is a very wide one, and this is especially the case after the spectacular developments which have occurred during the past few years. In the time at our disposal it will be necessary to limit ourselves to certain selected topics. I shall, for example, say nothing about arsenicals or anthelmintics, about antimony or bismuth derivatives; not because these are unimportant or because no advances have been

made during the past ten years—every month new papers and patents appear on all these topics—but because other branches of the subject clamour even more insistently for inclusion. You will note, then, that I am deliberately excluding, *inter alia*, all the organo-metallic compounds, all those chemotherapeutic agents which contain metals or metalloids, such as arsenic, antimony or bismuth, gold or silver, mercury or lead. A few years ago this would have been like presenting *Hamlet* without the "Prince of Denmark," for at that time the organic arsenicals were pre-eminent amongst synthetic chemotherapeutics. But, as you know, a new character has suddenly displaced the "Prince" from the centre of the stage: sulphur has succeeded arsenic as the predominant therapeutic element, and it is on the sulphonamides that attention is now most closely focussed.

It is not the purpose of this lecture to give a comprehensive account of even a small section of the subject of chemotherapy. Every month a large number of new papers are published, so that in this recently developed field of sulphonamides alone the literature is already immense It may be more useful, by discussing a few selected topics, to bring out some of the most striking features of this branch of science. As I have just stated, I shall limit this survey almost exclusively to the non-metallic compounds. Our discussion may conveniently be grouped under three heads: the antimalarials, the antitrypanosome drugs, and the antibacterial sulphonamides.

ANTIMALARIALS

As you know, three chemical compounds are chiefly employed at present as antimalarials One of these is a natural product, and the other two are synthetic: they are quinine, plasmoquine and atebrine, and their chemical structures are shown in Figs. 1, 2 and 3 We at once note certain features common to all three structures. They are all derivatives of the simple compound quinoline (Fig. 4), and they all carry a side-chain containing a dozen or so carbon atoms, twenty or so hydrogen atoms, and one or two nitrogen atoms All of them contain a methoxyl group in the same position in the quinoline nucleus These features are common, not only to these three compounds, but to many other active derivatives which may be considered as minor modifications of one or other of these three types, as well as to a few other distinct active types which have been discovered more recently and which I shall refer to later. Unfortunately, it is

only a very small fraction indeed of the large group of compounds possessing these common properties that exhibit antimalarial activity. As we shall see, quite small changes of structure may very much reduce or completely abolish the action.

FIG 1.—Quinine.

FIG. 2.—Plasmoquine.

FIG. 3.—Atebrine.

FIG. 4.—Quinoline.

FIG. 5.—Acridine.

FIG. 6.

The differences between these three compounds are perhaps more noteworthy than their resemblances. Though all three are in a sense derivatives of quinoline, atebrine is more naturally regarded as a derivative of acridine (Fig. 5), a ring system containing one pyridine and two benzene rings. Atebrine is peculiar, also, in containing a chlorine atom attached to one of the benzene rings, and the presence of this chlorine atom is very important for its chemotherapeutic activity; if it is not present, but is replaced by hydrogen, the activity is effectively lost. The basic side-chains in atebrine and plasmoquine are identical in structure, but they are attached to different positions of the quinoline nucleus. The side-chain of quinine has an altogether different structure; it contains one instead of two nitrogen atoms, is of the nature of a bridged ring instead of an open chain, and is attached to the quinoline nucleus, not by its nitrogen atom, but by one of its carbon atoms. Furthermore, this carbon atom is of a type which is absent from the other two compounds; it has attached to it a hydrogen and a hydroxyl group, and it has been shown that if these groups are in any way modified, as by replacing the hydroxyl by hydrogen or chlorine, the activity of the compound is completely lost These differences seem all the more singular when we remember that it is quinine and atebrine which are schizonticidal, and plasmoquine which is gametocidal; for, amongst these three compounds, it is perhaps between quinine and atebrine that the differences of chemical structure are most marked.

A great deal of careful work has been done on the effect of introducing slight modifications into the structure of these three compounds Sometimes, as in the case of the removal of the chlorine atom of atebrine mentioned above, relatively small changes in structure produce altogether disproportional changes in chemotherapeutic properties. Frequently, as when we lengthen or shorten the side-chain, we obtain a less drastic and more regular alteration in activity In all three compounds the removal of the methoxyl group results in a substantial decrease in antimalarial potency. The large amount of work that has been done on this question of the effect of small variations is of value for two reasons, through it, we may hope ultimately to be able to deduce rules relating structure to chemotherapeutic activity, and, secondly, it is only through such work that we can at present hope to solve the practical problem of discovering the most efficient compound of the type under consideration. With regard to the first of these reasons, we must confess that at

present broad generalisations are still lacking and only a few rules of limited applicability are known.

We have then three families of antimalarial compounds, all the members of each family being of one type, the quinine type, the plasmoquine type, or the atebrine type. The various members of each family differ only slightly from each other in chemical structure, but one or two members of the group may be outstanding as far as chemotherapeutic activity is concerned. Now, one of the most important events in chemotherapy is the discovery of a new family of active compounds. Once a member of such a new family has been found to be active, a whole new field is opened up. The activity detected in the first member of the family may only be very slight, but the organic chemist is able to synthesise many similar compounds, with all sorts of minor modifications of structure, and there is a very considerable chance that, sooner or later, some compound belonging to the family may be discovered of really high activity. This search for new types of active compounds is a very important part of the field of chemotherapeutic research. At present the worker in this branch of the subject is handicapped by the fact that so far, in spite of many efforts, no rational theory of chemotherapeutic activity of general application has been developed. We are not yet in a position, before we begin our syntheses, to work out on paper the structure of a compound which we can predict beforehand will be active We are driven to the expedient of working more or less systematically over certain fields suggested to us by some vague hint or analogy. The result is, of course, that most of the tickets we draw in the lottery prove to be blank; but if we do happen to be lucky and hit upon a winner, the success may turn out to be of the greatest practical importance.

We enquire, then, whether any families of compounds with antimalarial activity have been discovered other than the three already mentioned The answer is that several have been detected, but that so far none of them has achieved practical importance in the treatment of human malaria One of these families consists of the sulphonamide drugs, concerning which there is now a considerable body of evidence that they possess definite though rather weak antimalarial activity, especially against *plasmodium vivax* as well as against various avian malaria parasites. Another novel type of antimalarial drug is that represented by undecanediamidine (Fig. 16), which belongs to a family of which the antitrypanocidal potency has recently been discovered, and which

will be discussed more fully in the next section. A third type of new antimalarial drug was discovered a few years ago by the Russian workers, Magidson and Rubzov, who found that the compound represented in Fig. 6 was active. As will be seen, the side-chain present in this compound is the same as that present in plasmoquine, but it is inserted in the same position in the quinoline nucleus as the side-chain in quinine. In a sense, then, it may be regarded as a hybrid between quinine and plasmoquine.

In a very recent paper it is stated that this compound, like quinine and atebrine, acts on the schizonts and not on the gametes of the malarial parasites. Magidson and Rubzov found that a very slight modification of the structure, the mere introduction of a methyl group into position 2 (marked with an asterisk) of the quinoline nucleus, completely abolished the activity. It is appropriate here to draw attention to the many valuable papers which have been published during the past decade by Magidson and his colleagues. These constitute a very welcome contribution to our knowledge of the chemistry and chemotherapeutic action of synthetic antimalarials.

The last group of compounds with antimalarial activity to which I shall refer is that recently synthesised by Dr Harold King and his co-workers. They found that the two compounds represented in Figs. 7 and 8, and also a few closely related

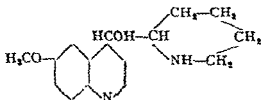


Fig 7

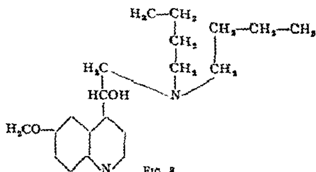


Fig. 8

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We have then three families of antimalarial compounds, all the members of each family being of one type, the quinine type, the plasmoquine type, or the atebrine type. The various members of each family differ only slightly from each other in chemical structure, but one or two members of the group may be outstanding as far as chemotherapeutic activity is concerned. Now, one of the most important events in chemotherapy is the discovery of a new family of active compounds. Once a member of such a new family has been found to be active, a whole new field is opened up. The activity detected in the first member of the family may only be very slight, but the organic chemist is able to synthesise many similar compounds, with all sorts of minor modifications of structure, and there is a very considerable chance that, sooner or later, some compound belonging to the family may be discovered of really high activity. This search for new types of active compounds is a very important part of the field of chemotherapeutic research. At present the worker in this branch of the subject is handicapped by the fact that so far, in spite of many efforts, no rational theory of chemotherapeutic activity of general application has been developed. We are not yet in a position, before we begin our syntheses, to work out on paper the structure of a compound which we can predict beforehand will be active. We are driven to the expedient of working more or less systematically over certain fields suggested to us by some vague hint or analogy The result is, of course, that most of the tickets we draw in the lottery prove to be blank; but if we do happen to be lucky and hit upon a winner, the success may turn out to be of the greatest practical importance.

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may form the point of departure for much further work, and they may well be regarded as constituting distinct types of antimalarials.

Trypanocides

When we survey the formulæ of drugs with trypanocidal activity we meet with a situation closely resembling that found in the case of the antimalarials. Many trypanocidal compounds are known, but they belong to a comparatively small number of types. The various types, however, show an even wider range of chemical structure than do the known compounds of antimalarial activity. If we limit ourselves to compounds of one type, the activity is often very markedly influenced by relatively small changes of constitution. This situation is met with, not only in relation to antimalarials and trypanocides, but in most other branches of chemotherapy as well. Indeed, we encounter the same type of phenomena in connection with carcinogenic or œstrogenic compounds. Carcinogenic compounds, for example, belong to quite a number of very distinct chemical types; some are azo-dyestuffs, others are styrylquinolines, others pure hydrocarbons, and so on. And yet, within each group, the carcinogenic activity is highly sensitive to small changes of structure. It is as if the normal processes of cellular metabolism could be disturbed at any one of a number of key points, each point being open to attack by compounds of a highly specific structure. Any significant deviation from this structure renders the compound harmless. In chemotherapy it is a lethal attack on key positions in the parasite that is aimed at. From this point of view we see that there is a parallel between carcinogenic and chemotherapeutic action on the biological side, and it is possible that this similarity may hold for œstrogenic action as well.

Several typical compounds exhibiting trypanocidal activity are represented in Figs. 11 to 19 The wide variation in chemical structure will be at once recognised These do not include any

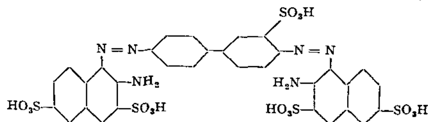


Fig 11.—Trypan red

compounds, possessed antimalarial activity. These structures are more closely related to that of quinine than is the case with any other of the synthetic antimalarials. They may be regarded as derived from quinine by breaking up the side group in that alkaloid, as shown by the dotted lines in Figs. 9 and 10. Indeed,

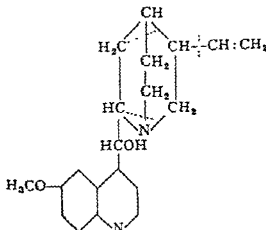


Fig 9.

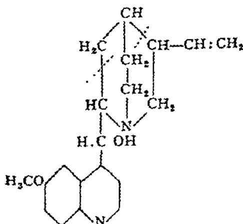


Fig 10

it was in an effort to obtain an active compound of the quinine type but of the simplest possible structure that King and his colleagues came to synthesise these compounds. *However, the* disappearance of the bridged ring, so characteristic of quinine, is a very considerable structural modification. It is found that quite small changes introduced into the structures 9 or 10 may result in complete loss of activity. Evidently these new compounds

(Fig. 11). As will be seen, this consists of a number of benzene and naphthalene rings joined by the azo- or —N : N— linkage. The idea was conceived of replacing this connecting link by the amide group, and, after a very large amount of research, presumably on the trial and error principle, the singularly active compound, Bayer 205, was ultimately arrived at. Though colourless, it retains the property of its azo-dyestuff prototype of being readily adsorbed on cotton fibre, and has indeed been termed a colourless dye. As you know, it has established itself as a most important weapon in the fight against sleeping sickness, being highly effective in the earlier, though not in the later, stages of

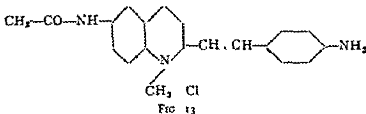


Fig 13

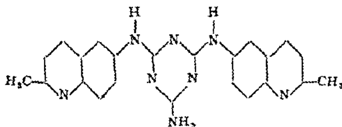


Fig. 14 —Surfen C

the disease. Once the parasites have established themselves in the central nervous system, the drug is of little use, presumably because of the difficulty of penetrating to the brain and spinal cord.

The most recently discovered of the trypanocidal drugs are the diamidines. The chemotherapeutic properties of these compounds have been brought to light during the past few years The history of their discovery well illustrates the curious way in which advances in chemotherapy are often achieved. It was observed that trypanosomes *in vitro* take up large quantities of oxygen in presence of glucose, and that they rapidly die when glucose is lacking. Administration of insulin was shown to reduce the rate of multiplication of the parasites *in vivo* and to prolong the life of the host. It seemed that any method of

organo-metallic compounds; many derivatives of arsenic and antimony have a very powerful antitrypanosome action. This rich assortment of trypanocidal compounds seems to have no property in common other than the biological one which characterises it.

Of all these drugs, that known originally as Bayer 205 (Fig. 12) is in some respects one of the most remarkable of therapeutic agents. It is now known as Germanin in Germany, Moranyl in France, and Antrypol in Great Britain. As will be seen from its structural formula (Fig. 12), it has an altogether bigger molecule than any of the other chemotherapeutics in common use. It contains no very characteristic group analogous to the basic side-chains in the synthetic antimalarials, or the sulphonamide group in the new antibacterial drugs And yet its whole structure is an altogether peculiar one, with its benzene and naphthalene

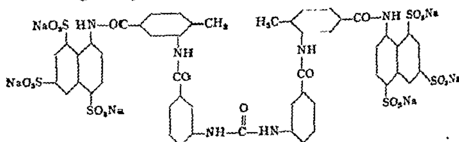


FIG. 12.—Bayer 205.

rings joined by amide linkages, the same kind of linkage as forms the backbone of the protein molecule. If into this huge structure a relatively slight modification is introduced, the omission or change of position of a methyl group, or the alteration of the position of attachment of the amide linkages, the anti-trypanosome activity of the compound is much decreased, or completely abolished. The large size of the molecule suggests that this compound acts more probably by adsorption on the surface of the parasite than by penetrating freely into it. It seems to have a peculiar affinity for certain proteins, and it has the interesting property of inhibiting blood coagulation The most probable explanation of its activity would seem to be that it interferes specifically with some important enzyme system in the trypanosome; v Jansco and v. Jansco suggest that the sugar metabolism may be particularly involved.

Bayer 205 seems to have been originally prepared on the analogy of certain trypanocidal azo-dyestuffs such as trypan red

far, no compound of this group has given promise of being important for the treatment of human malaria, but the history of chemotherapy suggests that further research may well produce related compounds valuable as medicaments in the human disease.

The other important development of this recent work on diamidines has been the discovery that some of these compounds

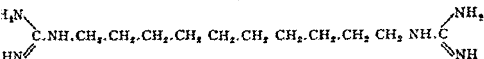


Fig. 15.—Synthalin

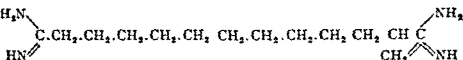


Fig. 16—Undecanediamidine.

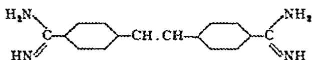


Fig. 17—p-p'-Diamidinostilbene

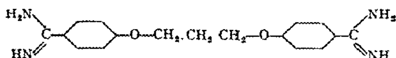


Fig 18—p-p'-Diamidinodiphenoxypropane

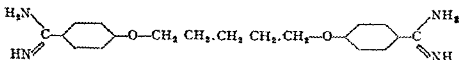


Fig 19—p p'-Diamidinodiphenoxypentane

are very valuable in the treatment of human kala azar. So far, the compounds chiefly tried have been the three represented in Figs. 17, 18 and 19, and they seem to be highly effective in both the Indian and Mediterranean varieties of the disease. Perhaps future research may discover compounds of the series even more potent than any of the three mentioned above, but, apart from this possibility, the results already obtained are of immediate practical significance.

reducing the blood sugar might result in conditions for the trypanosomes becoming difficult and so the chance of the patient's survival being increased. Soon after the discovery of insulin, synthalin was put on the market as a compound of known constitution which would reduce the blood-sugar level (Fig. 15). It was soon shown that it was of no real good for the treatment of diabetes, for it acted, not like insulin, by promoting sugar metabolism, but rather as a poison, preventing liberation of sugar from the liver into the blood-stream. However, it was possible that synthalin, which did undoubtedly lower the blood-sugar level, might, on the above theory, exert an antitrypanosome action.

It was tried and proved effective. However, it was soon shown by Lourie and Yorke that the action of this drug was a direct one on the parasites, as they were killed by it *in vitro* at concentrations of 1 in 250,000,000. The hypothesis was wrong, but it had led to the discovery of a new class of trypanocidal compounds, the diguanidines; for synthalin (Fig. 15) consists of a long chain of carbon atoms with a guanidine group at each end. Other closely related diguanidines were also active, but even better results were obtained by the somewhat closely similar diamidines which were prepared and tested by King, Lourie and Yorke, of which a typical example is shown in Fig. 16. The great promise of these diamidines has resulted in considerable work being devoted to their investigation. Both King and Ewins and their collaborators have found that the two amidine groups may be separated by aromatic as well as by purely aliphatic structures. Of the compounds prepared by Ewins, diamidinostilbene (Fig 17), *p*-*p*'-diamidinodiphenoxypropane (Fig. 18), and *p*-*p*'-diamidinodiphenoxypentane (Fig. 19) are amongst the most active. These compounds are still too new to have been tested out very completely on human trypanosomiasis, but preliminary reports appear very promising.

This investigation on antitrypanosome drugs of the diamidine series has had two incidental results, one suggesting future possibilities, the other of immediate practical value. The first has already been referred to when discussing antimalarials Amongst the diamidines reported on by King, Lourie and Yorke, undecanediamidine (Fig. 16) was highly active It was tested not only for trypanicidal but also for antimalarial activity. When a positive result was obtained, it was obvious that a new type of antimalarial had been discovered, for this compound is completely distinct from any of the other known types of antimalarials. So

far, no compound of this group has given promise of being important for the treatment of human malaria, but the history of chemotherapy suggests that further research may well produce related compounds valuable as medicaments in the human disease.

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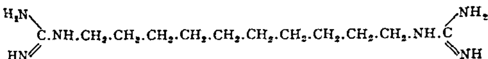


Fig 15.—Synthalin.

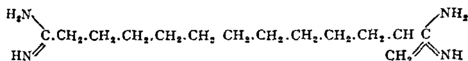


Fig. 16 —Undecanediamidine

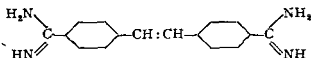


Fig. 17.—*p p'*-Diamidinostilbene

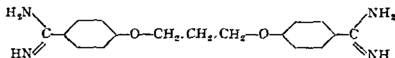


Fig. 18.—*p-p'*-Diamidinodiphenoxypropane

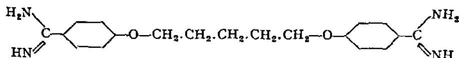


Fig. 19 —*p-p'*-Diamidinodiphenoxypentane

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Chemotherapy of Bacterial Diseases: the Sulphonamides

As I have already mentioned, it was in relation to diseases due to protozoa that Ehrlich first developed the methods of chemotherapy. In view of the successes he soon obtained, it is not surprising that much effort should have been devoted to the problem of discovering chemical agents which should be effective against bacterial diseases. As is well known, Morgenroth at an early date found that certain quinine derivatives, such as ethyl dihydrocupreine (optochin), was efficient against pneumonia in mice, and these compounds were naturally given a wide clinical trial. However, the results were disappointing, and efforts were concentrated on the development of serum therapy rather than chemotherapy for the treatment of human pneumonia. With other bacterial diseases, chemotherapy was even less successful, and despite much work that had been done, the outlook ten years ago seemed bleak and discouraging.

The whole situation underwent a dramatic change when, in 1935, it was announced by Domagk that certain dyestuffs containing a sulphonamide group cured some bacterial infections. From this point onwards progress was rapid. *It was* shown by the work of Tréfouël, Tréfouël, Nitti, and Bovet that the dyestuff as such was not essential, and that *p*-aminobenzenesulphonamide (Fig. 20) (sulphanilamide), to which the dyestuff



Fig 20.—Sulphanilamide.

is reduced in the organism, is equally curative. This compound had been known for many years; it was first prepared by Gelmo in 1908, but its peculiar therapeutic virtues were entirely unsuspected. But for the mere chance that Domagk happened to test out a dyestuff having a sulphonamide attached to it in a particular position, sulphanilamide and its derivatives might have remained chemotherapeutic gems, buried, not perhaps in "the dark unfathomed caves of ocean," but in the pages of Beilstein and the dusty store cupboards of the organic chemists.

We shall now glance very briefly over this great new field. It will be quite impossible to give even the sketchiest summary of the enormous literature which has appeared during the past few years. I shall leave the clinical aspects severely alone, and

try rather to emphasise some of the results which seem of significance for the science of chemotherapy in general.

During recent years a vast amount of effort has been put into the synthesis of new sulphonamide derivatives. Hundreds, perhaps thousands, of these have been prepared by the organic chemist; a considerable number have proved to be active, a few have been applied in clinical practice. The active compounds may conveniently be divided into three classes. The first class consists of those compounds which probably give rise to sulphanilamide in the animal organism, so that the action is essentially that of sulphanilamide itself. This group includes

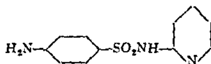


FIG. 21.—Sulphapyridine.

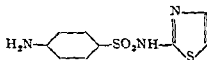


FIG. 22.—Sulphathiazole.

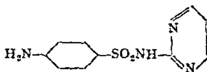


FIG. 23.—Sulphadiazine.

the original "prontosil" dyestuffs, to which we have already referred; soluseptasine (benzylsulphanilamide) is probably also in this category; whilst many modifications of sulphanilamide, more soluble than the original compound or possessing some other advantage, are also included.

The second class consists of compounds such as sulphapyridine (Fig. 21), sulphathiazole (Fig. 22), and sulphadiazine (Fig. 23) In these three compounds one of the hydrogens of the SO_2NH_2 group has been replaced by a particular atomic structure. These compounds have therapeutic potencies not possessed by the parent sulphanilamide itself. Broadly speaking, the latter is of use clinically in streptococcal infections, sulphapyridine acts on pneumococci as well, whilst sulphathiazole has a more definite action on staphylococci than any of the others.

Sulphadiazine appears to be comparable with sulphathiazole in bactericidal power, whilst it has the further advantage that with it a relatively high blood concentration is easily attained, apparently in consequence of the slowness of the rate of elimination by the kidneys. Amongst other compounds of this type which have been made recently, we may mention sulphapyrazine (Fig. 24), and sulphathiazoline (Fig. 25), in which other ring systems have been introduced into the molecule, but these compounds have not yet found clinical application. There are, however, two widely used compounds which may belong to this class—at least they are

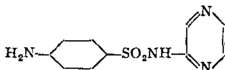


Fig. 24.—Sulphapyrazine

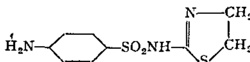


Fig. 25.—Sulphathiazoline

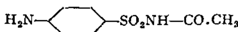


Fig. 26.—Sulphacetamide.

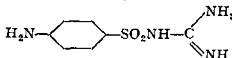


Fig. 27.—Sulphaguanidine.

derived from sulphanilamide by replacement of the H in the SO_2NH group. These are sulphacetamide and sulphaguanidine *(Figs. 26 and 27). The first forms a very convenient neutral* sodium salt which is highly soluble in water, whilst the latter is insoluble and not easily absorbed from the intestine; hence its use in the treatment of intestinal infections. Apart from their special physical properties, these two compounds may owe some of their chemotherapeutic virtue to their acting as such, and not after conversion into sulphanilamide, but of this we are not quite certain.

In the third class are included certain chemotherapeutically active compounds which, though carrying no sulphonamide group, contain a sulphur atom and are obviously related to the sulphonamides chemotherapeutically. An example of this class is

p-p'-diaminodiphenylsulphone (Fig. 28), in which, as in sulphanilamide, an SO_2 group is present, but here it is attached directly to two benzene rings, instead of to one benzene ring and to a nitrogen atom. This compound is curative against, for example, hæmolytic streptococci in considerably smaller doses than is sulphanilamide itself, but it is also proportionately more toxic to the animal organism. No compound of this third class has yet been widely used in practice, but it is always possible that some member of it may be found of special value and suddenly spring into the limelight. Already certain derivatives of *p-p'*-diaminodiphenylsulphone into which chemical groups have been introduced with the object of increasing solubility and decreasing toxicity have given encouraging results in the treatment of tuberculosis. It is surprising that these sulphones, which differ chemically so much from the true sulphanilamide derivatives, should share their chemotherapeutic properties when such small chemical modifications produce inactivity, but this is only another example of the type of anomaly we have already encountered in discussing the antimalarial and the trypanocidal drugs.

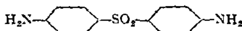


Fig 28 —*p-p'*-Diaminodiphenylsulphone

The explanation of these anomalies will no doubt become clear once we have some real insight into the mode of action of chemotherapeutic substances. The chief weakness of the subject at the present time is its almost exclusively empirical character. From the practical point of view it has achieved much, it has "delivered the goods" One disease after another has proved vulnerable to its weapons, and now it is only with the virus diseases that little progress has been made But in a satisfactory development of a science the practical and the theoretical sides should advance *pari passu*. When we turn to the theoretical side of chemotherapy, we find few important advances to record, in spite of the many efforts that have been made to increase knowledge in this field. No principles have been laid down that might tell us *a priori* which types of compounds shall be active in any particular disease. We cannot with any confidence state why the active compounds are active. In most cases we have little idea of the precise way in which the chemotherapeutic agent gets in its blow at the parasite, the exact vital process within the organism which is interfered with by the drug.

This backward position of chemotherapy on its theoretical side is all the more remarkable when it is remembered that Ehrlich blazed the trail under the inspiration of very definite theoretical conceptions. These were derived from his ideas in the related field of immunology. He conceived of his substances, immunological or chemotherapeutical, as organic molecules, carrying various groups, each of which exercised definite and essential properties. One was a group which would promote the attachment of the compound to the tissue of the organism; another was a group which would exert a toxic action on this tissue when brought into close contact with it. If the first group were properly chosen, the compound would be concentrated on the parasite's, rather than on the host's tissue. Thus the essential specificity could be attained. This theory, though it undoubtedly guided Ehrlich in his brilliantly successful work, was too vague and hypothetical for general application But for many years little real advance on it was made. It is one of the gratifying results of the discovery of the sulphonamides that, in relation to these compounds, indications have been obtained of the type of chemical mechanism in the organism on which they exert their effect. For the first time we seem to be able to detect the exact spot where the chemotherapeutic arrow hits its mark.

Early in the course of investigations on the mode of action of sulphanilamide it was ascertained that this compound exerted a definite bacteriostatic effect *in vitro* on the organisms which it destroyed *in vivo*. The precise relation of this bacteriostatic action to the curative effect we shall discuss later; meanwhile we shall review the steps which have led to a very plausible hypothesis as to the precise chemical mechanism whereby the sulphonamide compounds exert their action on susceptible bacteria. I have endeavoured to include a fairly complete bibliography of this important aspect of the subject up to the date of writing (May 1942)

Reports soon began to appear that the bacteriostatic effect of sulphanilamide might be inhibited under certain circumstances. Lockwood (1938) reported that peptone, even in small amounts, much reduced the bacteriostatic action on streptococci. It was, however, Stamp (1939) who made the important observation that extracts of hæmolytic streptococci with dilute ammonia contained a principle powerfully antagonistic to the bacteriostatic action of sulphanilamide and sulphapyridine.

At about this time Fildes and his school were busy developing

a theory of antiseptics which he had proposed. According to this theory, an antiseptic acts through interfering with some essential metabolite in the bacterial cell, that is to say, by preventing the proper functioning of some particular chemical compound, or special chemical group indispensable for the life of the cell. This idea as applied to chemotherapy was not altogether new; investigators such as Voegtlin and King have suggested that the organic arsenicals produce their biological effect by acting in the arsenoxide form, and combining with the free $-SH$ groups of the cells according to the equation $RAsO + 2HSR' = RAs(SR')_2 + H_2O$. It is of interest to notice that, as early as 1908, Ehrlich suggested that arsenicals might react with tissues through the $-SH$ groups of the latter. Fildes (1940 (1)) adduced experimental evidence in favour of the idea that mercuric salts exerted their bactericidal effect in an analogous manner, that is by combining with the free $-SH$ groups, the main evidence being that the effect of the Hg ions was antagonised by an approximately equivalent amount of a compound containing $-SH$ such as glutathione, which would compete for the Hg. If the sulphonamides acted similarly, through interfering with an essential metabolite, then their bacteriostatic effects might be expected to be antagonised by the presence of a sufficient excess of this metabolite. Many of the known essential metabolites were therefore tested without positive result.

Stamp's observations, however, suggested a clue, and Woods, working with Fildes (Woods and Fildes, 1940, Woods, 1940), found that by applying the method of extraction with dilute ammonia to yeast, extracts were obtained relatively very rich in the factor which antagonised the bacteriostatic action of sulphanilamide. In a remarkably complete and well-written paper, Woods (1940) describes the purification of the crude yeast extracts, and, though he did not succeed in isolating the active material, he was able to reach important conclusions about its chemical nature from experiments on his concentrated and purified solutions.

Now Fildes (1940) (2) had suggested that the bactericidal agent might interfere with an essential metabolite, not necessarily by combining with it as in the case of Hg and the $-SH$ group, but through some other mechanism For example, the essential metabolite might be the substrate of an enzyme (that is, the compound on which the enzyme acts), and the agent might interfere by displacing the proper substrate from the active

positions on the enzyme molecule. The enzyme would thus be blocked and unable to act on the real substrate; it is rather like jamming a lock with a key which almost fits but does not quite. We know of a number of examples of the blocking of enzymes in this way; the inactivating compound always bears a certain resemblance to the normal substrate, so that it can take the place of the latter on the enzyme surface, but must differ sufficiently to be unable to complete the reaction in question. We recall the interesting example of choline esterase which, like simple esterases, is inhibited by physostigmine and certain related compounds. These carry a urethane group, which has a certain resemblance to an ester group; such a compound can displace the esters from the esterase, but not being a true ester, it cannot undergo hydrolysis, but remains, blocking the enzyme and inhibiting its action As was shown mainly by the work of Loewi and of Stedman, it is apparently by thus inactivating the choline esterase in the body and allowing acetylcholine to accumulate that physostigmine and its synthetic analogues, such as myostigmine, exert their physiological effects. An overdose of physostigmine, in fact, poisons the body by competing with the essential metabolite, acetylcholine, for the enzyme, choline esterase, of which acetylcholine is the proper substrate.

It seemed possible that the compound antagonising sulphanilamide present in the yeast extracts might be an essential metabolite normally functioning in the bacterial cell, and that sulphanilamide produced bacteriostasis by competing for, and so blocking, an enzyme normally acting on this metabolite. In these circumstances, excess of the metabolite might be expected to displace the sulphanilamide from the enzyme and so restore the cell to its normal functional activity As mentioned above, the blocking compound and the normal substrate must resemble each other in chemical structure; it follows that the unknown hypothetical metabolite must resemble the enzyme inactivator sulphanilamide.

The chemical evidence obtained by Woods indicated that the compound was a stable substance of relatively low molecular weight, and that it had an amino and a carboxyl group. The simplest compound with these properties, and also resembling sulphanilamide, was *p*-aminobenzoic acid (Fig. 29) This compound was therefore tested, and was found to antagonise the bacteriostatic action of sulphanilamide in exceedingly minute amounts. Not only did it neutralise the bacteriostatic action of sulphonamide derivatives *in vitro*, but, as Selbie (1940) showed,

it also abolished the curative power of these drugs *in vivo*, a result afterwards confirmed by other workers (Findlay, 1940; McCarty, (1941).

Woods prudently pointed out that, though the circumstantial evidence was strong that *p*-aminobenzoic acid was the antagonising agent actually present in the yeast extract, the possibility of some closely related compound being the naturally occurring substance could not be excluded. Subsequent work has, however, made it abundantly clear that *p*-aminobenzoic acid itself is an important constituent of most bacteria, and probably of many other forms of living matter, and that it plays an essential rôle in metabolism. Thus Rubbo and Gillespie (1940) isolated this acid as its benzoyl derivative from yeast extracts, and they also showed (1940, 1942) that in the case of *clostridium acetobutylicum* it not only antagonised the bacteriostatic action of sulphonamide derivatives,



FIG. 20.—Sulphanilamide



FIG 29 —*p*-Aminobenzoic acid.

but also acted as an essential growth factor. The fact that it is not a growth factor for streptococci only means that these bacteria can normally synthesise it sufficiently rapidly to dispense with extraneous supplies. It has been found to antagonise the inhibiting action of sulphanilamide, not only on bacteria, but on yeasts grown on a suitable synthetic medium (Landy and Dicken, 1942), as well as on the dermatophytic fungus, *trychophyton purpurem* (Dimond, 1941), and even on the autotrophic diatom, *Nitzschia palea* var. *debilis* (Wiedling, 1941).

These observations indicate the importance of *p*-aminobenzoic acid in the metabolism of many micro-organisms The fact that the animal organism is relatively insensitive to the presence of considerable concentrations of the sulphonamide drugs suggests that *p*-aminobenzoic acid does not play so vital a rôle in animal tissue. However, it seems that it has an importance here also, for Ansbacher (1941) and Ansbacher and Martin (1941) have claimed that it acts as an anti-grey-hair (chromotrichia) vitamin of

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FIG. 20.—Sulphanilamide.

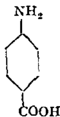


FIG 29 —*p*-Aminobenzoic acid.

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rats, and as a growth factor for chicks, whilst the work of Sure (1941) suggests that it may be required for normal fertility and lactation. It is in harmony with these findings that extracts of certain animal tissues have been found to contain a factor, presumably *p*-aminobenzoic acid, antagonising sulphanilamide.

As an antagonist to sulphanilamide bacteriostasis, *p*-aminobenzoic acid shows itself peculiarly effective, for one molecule may neutralise the effect of up to 25,000 molecules of the latter drug acting on streptococci (Woods, 1940). With sulphapyridine the efficiency is somewhat less, the ratio here being 1 to 5000 Comparable results have been obtained by Landy and Wyeno (1941) for streptococci with sulphanilamide, pneumococci with sulphapyridine, and staphylococci with sulphathiazole. In studying the growth of pneumococci in blood-broth, Strauss, Lowell and Finland (1941) found that the antagonistic action of *p*-aminobenzoic acid was most marked when sulphanilamide was used as bacteriostatic agent, less with sulphapyridine, and least of all with sulphathiazole.

The latter authors have also studied the absorption of *p*-aminobenzoic acid into the blood and its excretion by the kidneys in man. They show that the compound has no demonstrable action on the toxic effects of the sulphonamide drugs, a result in agreement with the findings of McCarty (1941).

Green (1940) obtained sulphanilamide-antagonising extracts from *Br. abortus*. Subsequent investigations by Green and Bielchowsky (1942) (1) showed that the extracts from these and certain other bacteria examined probably contained *p*-aminobenzoic acid as well as another factor which acted as a general stimulant of bacterial growth, and so antagonised the effect of sulphanilamide but in a non-specific manner. Similar results have been obtained by other workers (Loomis, Hubbard, and Neter, 1941). It seems generally agreed that *p*-aminobenzoic acid does not stimulate growth in the absence of inhibition by a sulphonamide compound, though, as mentioned above, it may act as a growth factor with organisms such as *Cl. acetobutylicum*, which are evidently deficient in their ability to synthesise it.

A number of compounds other than *p*-aminobenzoic acid also are able to antagonise sulphonamide derivatives (Woods, 1940). These include ethyl *p*-aminobenzoate, *p*-aminobenzamide, procaine, *p*-nitrobenzoic acid, and *p*-hydroxylaminobenzoic acid. These are all compounds which we might expect the cell to convert into *p*-aminobenzoic acid without much difficulty, and this

suggests that they do in fact act by being converted into the latter compound. Most of them are much less effective than *p*-aminobenzoic acid itself; only two of them, namely, procaine and *p*-hydroxylaminobenzoic acid, can exert their antagonising effect at concentrations comparable with those at which *p*-aminobenzoic acid is active. The former compound is probably very readily hydrolysed to its components, *p*-aminobenzoic acid and diethylaminoethanol, whilst the latter is presumably easily reduced to the amino-acid. It is just possible that the enzyme which is involved in sulphonamide action is one which promotes the interconversion of the hydroxylamino- and the amino-acid by a reversible oxydation-reduction reaction such as is characteristic of many processes in the living cell. There is, however, no experimental support for this guess. Very recently Auhagen (1943) has stated that with *Streptobacterium plantarum* *p*-aminobenzoyl-*l*-glutamic acid, *i.e.* the amide formed from *p*-aminobenzoic acid and *l*-glutamic acid, is 8-10 times more antagonistic to sulphanilamide than is *p*-aminobenzoic acid itself. If this is confirmed, it may prove an important clue to the rôle which *p*-aminobenzoic acid plays in metabolism. For an interesting comparison of some physical properties of *p*-aminobenzoic acid and sulphanilamide, see Albert and Goldacre, 1942.

We see, then, that within the last year or two a very considerable body of facts have been brought to light, all of which are in conformity with the hypothesis of Fildes and Woods that sulphanilamide and the related sulphonamides produce bacteriostasis by interfering with the metabolism of a structurally related compound, namely, *p*-aminobenzoic acid, through competing with it for an enzyme of which it is normally the substrate This hypothesis has resulted in the discovery of *p*-aminobenzoic acid as an essential metabolite for many, if not all, bacteria, for yeast, certain moulds, and other micro-organisms and as a vitamin in animal nutrition.

If this theory of Fildes is true, it should prove fruitful in still other directions. It should be possible to apply it in relation to essential metabolites other than *p*-aminobenzoic acid A general recipe for a new series of chemotherapeutics ought to be as follows: Take some essential metabolite or growth factor of known structure, synthesise a number of compounds of closely related constitution, and then use these against the bacteria for which the first compound is an essential metabolite. This formula has been followed by McIlwain and his colleagues with promising

results (McIlwain, 1940, 1941, 1942, McIlwain, Barnett and Robinson, 1942). Nicotinamide and pantothenic acid (Figs. 30 and 32) are known to be growth factors, and therefore presumably essential metabolites for streptococci and certain other organisms.

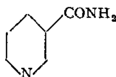


FIG. 30—Nicotinamide

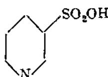


FIG. 31.—Pyridine-3-sulphonic Acid

These two compounds have been modified in various ways, but in particular by replacing the carboxyl or amide group by the sulphonic acid group. It is reported that the new compounds (Figs. 31 and 33) have the property of inhibiting the growth of bacteria in the sense that they neutralise the effect of the nicotinamide and pantothenic acid respectively. Of course, the efficiency

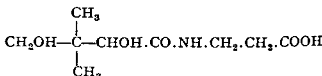


FIG. 32.—Pantothenic Acid

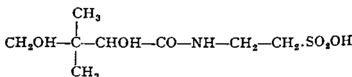


FIG 33.

of such compounds in the cure of disease will depend on the new agents being relatively non-toxic to the animal metabolism, and there is no guarantee that this will be so, but the success in pointing the way to the discovery of new bacteriostatic compounds is a striking confirmation of the theory and an encouraging promise of ultimate practical results. Recently McIlwain and Hawking (1943) have shown that rats infected with streptococcus hæmolyticus could be protected by the intensive administration of pantoyl taurin so that this compound, which is apparently non-toxic, may ultimately prove of clinical importance.

And now the question arises: Have we any idea as to what enzyme it is which normally has *p*-aminobenzoic acid as substrate

and which is blocked by sulphanilamide? A very suggestive observation has been made by Lipmann (1941), who has reported that hydrogen peroxide acts on *p*-aminobenzoic acid in presence of peroxidase, but that this enzymatic reaction is inhibited by sulphanilamide, as well as by sulphapyridine and sulphathiazole. Lipmann reports that the action of the peroxide-peroxidase system on other substrates, such as pyrogallol or tyramine, is also inhibited by sulphanilamide, and he recalls the previous announcement of Shinn, Main and Mellon, that catalase is inhibited by the drug. Fox (1942), who worked with *B coli*, obtained evidence that the enzymes affected by sulphanilamide may be concerned in the degradation of lactic acid, whilst Sevag and Shelbourne (1942), have shown that bacteriostatic action runs parallel in streptococci and pneumococci with inhibition of respiration.

In the above discussion it has been taken for granted that it is sulphanilamide itself which acts on the bacteria, and not, for example, some oxidation or reduction product The fact that the result of adding sulphanilamide to a growing culture of bacteria is to stop growth, not at once but only after a latent period of a few hours, suggests that a preliminary conversion to an active form may be necessary. Some writers have suggested that *p*-hydroxylaminobenzenesulphonamide (Fig 34) may be



Fig. 34 —*p*-Hydroxylaminobenzenesulphonamide.

the real active agent. Green and Bielschowsky (1942) (2) have investigated this point in a novel way. They assume that any bacteriostatic agent not antagonised by *p*-aminobenzoic acid is certainly not the active agent; in other words, only compounds antagonised by *p*-aminobenzoic acid can be considered as possible derivatives of sulphanilamide immediately responsible for the bacteriostatic action. They find that the action, neither of *p*-hydroxylaminobenzenesulphonamide nor of other oxidation products, is inhibited by *p*-aminobenzoic acid, and so conclude that no such oxidation product is likely to be the active agent formed from sulphanilamide in the cell. On the other hand, they find that various reduction products of sulphanilamide have a bacteriostatic action antagonised by *p*-aminobenzoic acid, and

suggest that, of all compounds examined, *p*-*p*'-diaminodiphenyldisulphide (Fig. 35) has the greatest claim to be regarded as the hypothetical active compound. However, everything considered, they think it most probable that it is sulphanilamide itself which competes with *p*-aminobenzoic acid for the enzyme, and that the assumption of an active product is unnecessary.

It must, of course, be remembered that the assumption that *p*-aminobenzoic acid is the substrate of an enzyme which is blocked by the sulphonamide drugs is still a hypothesis without rigorous proof. It correlates many facts, and has stimulated much interesting and fruitful experimental work. But that it is the only possible explanation of the action of the sulphonamides on bacteria has not been universally accepted. Johnson and Moore (1941) and Johnson (1942) have studied the action of sulphanilamide and *p*-aminobenzoic acid on luminescent bacteria.

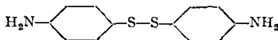


Fig 35—*p*-*p*'-Diaminodiphenyldisulphide.

Both growth and luminescence are stimulated by small, and inhibited by larger, amounts of urethane, *p*-aminobenzoic acid and sulphanilamide. The inhibitory effect of sulphanilamide on growth and luminescence is antagonised by urethane as well as by *p*-aminobenzoic acid. It is suggested that the antagonistic effects are examples of the neutralisation of one narcotic by small doses of another. Dorfman, Rice and Koser (1942) adduce evidence that the action of sulphapyridine and sulphathiazole are exerted through mechanisms different from that through which sulphanilamide itself works. None of these experimental findings are inconsistent with the correctness of the fundamental assumptions of the theory of Woods and Fildes, though it is possible that, in certain circumstances, complementary effects may be involved Clearly we must await further work in this field

The line of work just described seems to have established with reasonable certainty the mechanism whereby the drugs of the sulphonamide class exert their bacteriostatic action on the strains of bacteria which are susceptible to their presence. It seems likely that the inhibition of growth is but the outward expression of a disturbance of some important process in the organism's metabolism, and that, even though the bacterium is not killed, its vigour is impaired. The complementary part of the

explanation of the effectiveness of the sulphonamides we owe largely to Alexander Fleming. This work, indeed, was well on its way before the discoveries relating to *p*-aminobenzoic acid were made, and both lines of research, though complementary, stand on their own feet. Let us remark first of all that the mere bacteriostatic action of the sulphonamides in no way explains their chemotherapeutic efficiency. Many compounds are known which are not merely bacteriostatic, but highly bactericidal, in concentrations much smaller than those at which the sulphonamides are active. The latter act at concentrations of perhaps 1 in 50,000 or greater; substances such as proflavine will kill bacteria at concentrations less than one-tenth of this, and this even in the presence of serum or other body fluids. But proflavine will not cure hæmolytic streptococcal septicæmia or pneumonia, as sulphapyridine will.

Fleming showed that the effectiveness of the sulphonamides was closely dependent upon the presence of leucocytes. Though hæmolytic streptococci are not killed by sulphanilamide alone, in the presence of leucocytes plus the drug these bacteria are rapidly removed. The drug is like a dose of tear gas applied to a threatening mob, which enables a few policemen to deal with a situation otherwise quite outwith their power. The policemen are immune to the gas, or have masks to protect them, in other words, the leucocytes are in no way enfeebled by the sulphonamides. This indeed seems to be the key to the whole business. The ordinary bactericidal drug tends to injure the leucocytes as well as the bacteria, the sulphonamides paralyse the latter but leave *the former with their vigour unimpaired* These policemen are then able not only to mop up the mass of bacteria rendered powerless by the chemical, but if necessary to ferret out and kill the few which may, by lurking in corners, have escaped the toxic agent. In this way one great trouble in any attempt to affect destruction of infecting bacteria by chemical agents is overcome, namely, that a few of the bacteria are almost certain to escape and so soon multiply again once the drug disappears from the circulation.

Future Prospects

It is to Fleming, too, that we are indebted for opening up a new and most promising field. Some ten years or more ago he discovered that certain strains of the mould *penicillium* produced

a bactericidal agent which he called penicillin. Though the structure of this compound has not yet been ascertained—indeed, it is only in recent months that chemists have succeeded in obtaining the compound in a state of approximate purity—it seems clear that here we have a drug which combines high bactericidal power with exceedingly low toxicity to the animal organism. Once its structure is ascertained, it seems likely that a whole new field of chemotherapeutic importance will be opened to the synthetic organic chemist. Everyone is now familiar with the remarkable results achieved by penicillin and it would seem that the only drawback about this drug is the difficulty in obtaining it in anything like the quantities required to meet even the most urgent demands. Certain other products of bacterial mould or fungus origin, such as Patuline, have already been tried out in clinical practice and a degree of success has been claimed. But the importance of these products may turn out to be chiefly as guides to new types of active groupings which can be synthesised in the laboratory and modified so as to obtain still greater efficiency.

This work on penicillin is an example of research likely to lead to the discovery of new types of chemotherapeutic agents. An important and closely related aim is to bring within the scope of chemotherapy the various diseases which so far have not been successfully treated by the method. I have already mentioned that the early successes were attained against diseases due to protozoa and spirochætes. Bacterial infections remained resistant until the singular therapeutic efficiency of the sulphonamides was discovered Many important types of pathogenic bacteria were soon found to be vulnerable to the new weapons; hæmolytic streptococci, meningococci, gonococci, and pneumococci were all highly susceptible, and with the advent of sulphathiazole and sulphadiazine and now, of course, penicillin, there is hope that staphylococcal infections may also prove tractable. There are, of course, many claims on record of the successful treatment by the sulphonamide drugs of numerous other types of bacterial disease, ranging from colds and sore throats to tuberculosis and plague Many of these claims have been disputed or require confirmation, but progress in the subject is so rapid that there seems every reason to hope that, in the course of a few decades, the great majority of bacterial diseases will have been brought within the orbit of chemotherapy.

What of the virus diseases? Even in this group of infections

some encouraging results have already been obtained. Findlay has substantially reduced the death-rate from experimental *lymphogranuloma inguinalis* by means of sulphanilamide, and incidentally has shown that here, too, the curative effect of the drug is inhibited by *p*-aminobenzoic acid. Positive results have also been obtained in the treatment of human lymphogranuloma and of trachoma and other virus diseases. These successes, though less spectacular than those obtained with pneumococci or hæmolytic streptococci, are very encouraging, for they suggest that viruses are in no way invulnerable to chemotherapeutic attack, and if only we had a hint as to the right sort of chemical weapon to use, a great advance in curative medicine would very soon be effected.

So far, most of the great advances in chemotherapy have been due to chance observations or happy guesses; the new theoretical ideas developed by Fildes and his colleagues may in the future guide us with greater certainty into more fruitful lines of experimentation, and replace more or less random searching for new types of active compounds by a more economic procedure based on rational hypotheses.

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For a detailed account of chemotherapy with comprehensive references see "Recent Advances in Chemotherapy," by G. M. Findlay. (J. & A. Churchill Ltd. 2nd Edition, 1939)

THE CONTROL OF SEPSIS

By J. M. ROBSON, M.D., D.Sc.

(*From the Department of Pharmacology, University of Edinburgh*)

THIS is obviously a wide subject of which some aspects are at present of particular importance, namely, the sepsis associated with wounds and burns of some severity, to which this discussion will be restricted. Good surgery is, of course, of primary importance and indeed constitutes the first line of defence. Recent work has, moreover, emphasised the importance of rest, the value of which in helping the natural healing powers of the body was first fully realised by Hilton (1887). Trueta (1943) discusses these surgical factors in some detail.

There is no doubt, however, that chemical substances can play an important part in dealing with sepsis. The experience gained in the last war on the whole led to a loss of faith in this form of therapy, though important experimental advances were even then being made—for example, the investigations with quinine derivatives. This work, important historically and for the methods developed, is reviewed by Schnitzer (1925). The last few years have seen a revolution in our views concerning this problem, and this paper deals essentially with the value of chemical substances in the control of infection. A striking feature of the recent work is the demonstration of the value of prophylaxis; if effective treatment is started sufficiently early there is good hope of entirely preventing the development of sepsis in infected wounds. The report on the casualties treated at Pearl Harbour provides a striking example of this (Moorhead, 1942). Established sepsis, however, is still very difficult to deal with, but even here progress has been made.

Significance of Bacteria in Wounds

It is an obvious generalisation that infection delays the healing of wounds. In addition, toxic products are absorbed from the site of infection and produce a deleterious effect upon the body; this is, of course, of special importance in the case of infections with pathogenic anaerobes.

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Stages of Infection which have to be Treated

From a practical point of view we can consider the treatment of sepsis at three stages, each of which presents rather different problems.

1. *Immediate Disinfection* (within less than one hour after infection)—At this stage complete and rapid sterilisation of the infected area should be aimed at, and there is, indeed, good experimental evidence that all organisms in a wound can be destroyed by chemical substances provided that treatment be applied sufficiently early.

It should be noted, however, that even if a wound is completely sterilised there is a good possibility that it may become re-infected after the first twenty-four hours even when the most stringent precautions are taken, unless primary suture can be performed. Thus, for example, Cruickshank (1935) showed that the occurrence of hæmolytic streptococcal infection of third degree burns rose from 10 per cent. on admission to 66 per cent on the sixth day. Hence, even when complete sterilisation of a wound is possible, further bacteriostatic treatment is desirable to prevent reinfection unless the wound be closed. Indeed, some authorities believe that it is a desirable precaution to enclose a bacteriostatic agent in a sterilised wound even when this is sutured at operation.

2. *Delayed Disinfection* (after the immediate stage but before purulent sepsis is established)—Rapid and complete eradication of bacteria is now no longer possible The aim of the treatment should be to prevent multiplication of the organisms, which can then be dealt with by the natural defences of the body This bacteriostatic action is usually necessary over a fairly long period of time to ensure that all the organisms should be eradicated Early bacteriostatic treatment makes a great deal of difference to its ultimate success, and the first six hours following infection appear to be of crucial significance

3 *Treatment of Established Sepsis*—This is the most difficult problem and one which has so far defied complete solution. It is characterised by the presence of pus, which contains substances

Certain organisms found in infected wounds present a greater danger than others (Ogilvie, 1940); and since antiseptics and chemotherapeutic substances do not by any means act equally on all bacteria, it is of interest to consider which of these are commonly present in wounds and what their significance is.

Hæmolytic streptococci are a particular danger and are frequently found in wounds; they are, however, usually of low virulence when tested by the classical methods (Levaditi *et al.*, 1940) and this probably accounts for their low invasive properties. Pathogenic gas gangrene organisms are also an obvious danger, whilst other organisms frequently found, such as *Staphylococcus aureus*, *B. coli*, *B. pyocyaneus* and *B. proteus*, may provide a serious problem. Certain organisms which are often present in wounds are usually of little or no importance, for example, diphtheroids and *Staphylococcus albus*.

It is a remarkable fact that, though infection frequently interferes with the healing of wounds, normal healing may occur in the presence of so-called pathogenic organisms such as the hæmolytic streptococci (Levaditi *et al.*, 1940). This aspect of infection requires much further study. McClean *et al.* (1943), indeed, have attempted to devise tests based on the production of certain enzymes, for determining the pathogenicity of gas gangrene organisms found in wounds, and this method appears to be a hopeful approach to the problem.

Types of Actions which Drugs can produce on Bacteria

There are three main types of actions produced by drugs. These are not always clearly distinct since some substances may have more than one type of action.

(*a*) *Direct Toxic Effect on the Bacteria.*—This is the classical antiseptic action and is frequently brought about by an effect on the bacterial proteins

(*b*) *Bacteriostatic Action.*—The classical antiseptics will frequently inhibit the multiplication of bacteria when applied in low concentrations. Modern chemotherapeutic work has revealed that there are certain substances which produce a bacteriostatic action by an effect on the bacterial metabolism by substrate competition with an essential metabolite of the bacteria.

(*c*) *Reduction of Virulence.*—There seems good evidence for believing that certain substances can modify the virulence of micro-organisms without killing them or affecting their power

of reproduction. According to Browning (1943) brief contact of organisms with acriflavine may produce such an effect, while Levaditi and Giuntini (1940) have advanced evidence which suggests that the application of sulphonamides to wounds can reduce the virulence of hæmolytic streptococci present in them.

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3. *Treatment of Established Sepsis.*—This is the most difficult problem and one which has so far defied complete solution It is characterised by the presence of pus, which contains substances

which antagonise the action of some antiseptic and chemotherapeutic substances.

Main Substances to be Considered

A very large number of substances have been used in the prevention and treatment of infection. However, only a comparatively small number of these have proved to be of definite value.

It should be noted that the substances used should produce as little irritation as possible, since this in itself may increase the harmful effects of sepsis. It is also desirable that their action should be exerted in collaboration with the natural defences of the body. They certainly should not in any way interfere with these natural defences and, especially, they should not prevent the phagocytic action of leucocytes.

Whenever possible other measures should be taken to help the natural defences of the body. For example, as already mentioned, rest (in plaster if necessary) may prevent the spread of toxic substances and thus improve the effectiveness of the body defences.

The most important substances to be considered are as follows :—

(1) Acridine derivatives.
(2) Synthetic detergents.
(3) Sulphonamides.
(4) Di-amidines (especially propamidine).
(5) Penicillin (and possibly other bacterial and mould metabolic products).
(6) Preparations which release free chlorine.

In addition, various antibodies have of course proved of great value in combating some of the effects produced by anaerobic organisms

Certain complications which may occur in the use of some of these substances should be considered here.

Drug Resistance

This is not a new phenomenon and has already been observed in connection with the treatment of diseases caused by protozoa. After a certain period of treatment these organisms may become resistant to the action of the specific chemotherapeutic substance,

possibly through a process of selection. Similar phenomena have been observed in the treatment of bacterial conditions with chemotherapeutic substances. There is, for example, much evidence that bacteria may become resistant to sulphonamides In the use of these substances it is therefore desirable to use comparatively large initial doses in order to overcome the infecting organisms as rapidly as possible and thus prevent the development of resistant strains. Recent work also suggests that resistance may develop to the action of penicillin. Rammelkamp and Maxon (1942) have demonstrated this experimentally, and it also apparently occurred in some cases treated with penicillin by Florey and Florey (1943).

Drug Sensitivity

Another difficulty which may be encountered is that the patient may develop idiosyncrasy for the drugs and exhibit sensitivity phenomena following their administration. These are fairly common with sulphonamides and especially with sulphathiazole, which has otherwise proved so satisfactory a chemotherapeutic agent amongst the drugs of this class These sensitivity phenomena are more common when the drugs are given systemically, but they have also been observed following their local application. The reactions with sulphonamides are usually mild but can occasionally be quite severe. They can be minimised by limiting the doses and the duration of administration. Sensitivity phenomena have also been observed in the local use of acridines. Thus Makins (1922) reports that 8 per cent. of the cases treated with acriflavine showed skin irritation. The synthetic detergents may also produce skin irritation.

Because of the occurrence of drug resistance and drug sensitivity it is desirable to have available more than one group of substances capable of producing the same effect. It is then possible to change the method of attack when the organism becomes insensitive, or the host too sensitive, to one particular chemotherapeutic agent.

Methods of Administration

Three main methods have been used, namely :—

1. General administration The drug is usually given orally but occasionally by injection. The period of administration should be kept as short as possible.

2. By local application.

3. Combined, general and local.

The same drug need not necessarily be used for the general and local administration.

Local Application.—Much progress has been made recently in the use of chemotherapeutic substances with this form of therapy. It presents certain definite advantages. Much higher concentrations of the chemotherapeutic substance can be produced in the tissues than when the drug is given systemically. This applies especially to the sulphonamides and to penicillin. In addition, the concentration of the drug in the blood is kept low, so that toxic effects are rarely produced. A variety of new techniques has been developed and the drugs may be applied as follows :—

(*a*) In solution or suspension. The duration of action when so applied is usually short but may be prolonged by impregnating gauze or other suitable material. The concentration used should be such as to allow for any active material absorbed by the gauze, etc.

(*b*) Sprays have been found convenient by some workers, especially for application to burnt areas.

(*c*) Powders have been used extensively in an attempt to produce a prolonged effect by slow solution in the tissue fluids. There is, however, a tendency for the material to cake.

In the case of certain substances of low solubility such as sulphathiazole, very finely subdivided preparations (microcrystalline) have been made in order to obtain a more rapid solution and hence more rapid diffusion into the tissues.

(*d*) Various ointments, pastes and jellies containing the active material have been made up Their constitution should be such as to ensure the optimum rate of liberation of the active material. In first-aid applications, for example, the liberation should be comparatively rapid so that adequate chemotherapeutic concentrations should be quickly produced in the infected tissues. Such preparations should be left on for only short periods, and precautions must be taken to ensure that too much absorption of the active material does not occur, otherwise toxic effects may be produced. A slow and continuous liberation of the active substance should be the aim in a preparation used for more prolonged treatment

It is important to make sure that the bases used in the ointments or pastes should be non-irritant, since otherwise the tissues may

be damaged. It has, for example, been shown (Hawking, 1943) that many oils tend to cause delayed connective tissue reactions.

(*e*) Methods have been elaborated by which continuous or intermittent flow of a solution of the active material over the infected area can be produced. The Carrel-Dakin technique of irrigation was, of course, used extensively in the last war to produce this effect. More recently (Bunyan, 1941) the envelope method has been developed in which the wound or burnt area is totally enclosed in an envelope of oiled silk and can thus be bathed in the solution at regular intervals.

Immediate Disinfection

This can frequently be effected by purely surgical methods as, for example, by the removal of all infected tissues. In a number of cases, however, surgical methods alone are not sufficient. It would in any case be an advantage if chemical substances were available by the use of which disinfection of an area could be guaranteed Such a method would, in conjunction with the necessary surgical steps, be of great value as a preliminary to primary suture or, in wounds in which this is impossible, as a prelude to the use of bacteriostatic agents to prevent reinfection. Under field conditions, where surgical treatment may frequently have to be delayed, the immediate use of chemical substances may prove of particular value

It is important that substances used in such immediate disinfection should produce as little damage as possible to the tissues since this will tend to increase and not decrease the ultimate severity of the infection. This was classically demonstrated in the last war in wounds treated with carbolic acid

There is evidence that soap may act as a potent disinfectant. It can certainly be of value in the preliminary cleansing of the skin and wounds, and can remove a large number of infecting organisms both by cleansing and by bactericidal action (see Trueta, 1943, for details).

A number of synthetic detergents introduced recently appear to have advantages over soap and water Of the large number made (see Lane and Blank, 1942, for review), two have very recently been investigated for their action in wounds, namely, CTAB (cetyl trimethyl ammonium bromide) and cetyl pyridinium

bromide. The latter appears to be better than CTAB in that it tends to produce fewer sensitisation reactions (Barnes, 1942; Williams *et al.*, 1943).

The bactericidal action of these detergents is greatly inhibited by organic matter. It is suggested therefore that, after the cleansing action has been produced, a final application of the detergent should be made in order to sterilise the area. A further suggestion is that the detergent should be followed by the application of a bacteriostatic agent, such as sulphanilamide, to prevent reinfection, and also to deal with any organisms which may have withstood contact with the detergent.

In connection with the immediate sterilisation of infected areas the acridine derivatives introduced by Browning in 1917 require serious consideration. For there is, firstly, good experimental evidence that acridines can sterilise an area of tissue infected with virulent organisms, not only when applied immediately but even when applied after an interval sufficient for some penetration of the organism into the tissues (Browning, 1943; McIntosh and Selbie, 1942; Hawking, 1941).

These drugs have certain important characteristics. Firstly their activity, unlike that of certain powerful older antiseptics, is not decreased by the presence of serum, though it is often greatly decreased by pus; and secondly, they have a low toxicity to tissues, though not as low as that of some of the modern chemotherapeutic agents.

Acriflavine, a mixture of 2 8 diamino-acridine hydrochloride and its N-methyl derivative, was the first of these compounds to be used, but there is evidence that certain pure acridine derivatives have a lower toxicity than acriflavine (Russel and Falconer, 1941). Of these, proflavine (2 : 8 : diamino-acridine sulphate) has been used quite extensively, while 2 : 7 : diamino-acridine hydrochloride has been suggested more recently. Another compound, 5 · amino-acridine, has the advantage of not staining tissues, and also requires further investigation.

The acridines are of value only when applied locally and not when administered generally. They should, on the whole, not be used in concentrations greater than 0·1 per cent.

It is probable that these substances can totally disinfect wounds when applied sufficiently early and they can therefore be of value when a primary suture is possible. It has, however, also been found that when primary suture is not possible infection develops in spite of their continued use (Drummond and McNee,

1917). This appears to be due to reinfection which occurs in spite of the presence of the acridines

Delayed Disinfection

When immediate disinfection with or without primary suture is no longer possible the aim of the treatment should be to prevent multiplication of the organisms and allow the natural defences of the body to deal with them. Such a method is also desirable when a wound has to be kept open even after complete disinfection.

There is good experimental evidence that bacteriostatic agents are especially effective when applied within six to twelve hours after infection, and that their value is greatly decreased when there is much further delay (Robson and Scott, 1942, 1943). It cannot be too much stressed that these bacteriostatic agents, which are applied over fairly long periods, should have very low toxicity and not interfere with the healing processes.

The sulphonamides are probably the best drugs at present available in practice for dealing with this stage of infection, and there are many recent publications concerning their action (Colebrook *et al.*, 1941; Long, 1943). These drugs are usually applied locally, but it is sometimes desirable to give, in addition, a short course by mouth. This may help to prevent the spread of infection from its primary site. The general administration is limited in order to prevent toxic reactions and sensitisation, but the local therapy is usually continued until healing is complete.

A variety of sulphonamides and related compounds have been used Sulphanilamide, which is the cheapest of these drugs, has been employed very extensively, usually in the form of a powder which should be sterilised (for methods, see *Brit Med. Journ.*, 1943, i., 263). There has been some discussion about the correct quantity to use. The drug diffuses quite readily into the tissues, and toxic reactions resulting from its absorption have occurred when the quantities applied have been too large Long (1943) suggests the application of 0·05 to 0·1 gram per square inch according to the extent of the contamination. Keeping the powder moist will help to prevent caking.

Sulphathiazole powder has also been used extensively because of its greater chemotherapeutic activity as compared with sulphanilamide. It has a very low solubility and it is thus advisable to use the micro-crystalline preparation in order to obtain the optimum rate of penetration into the tissues (Hawking, 1942). Sulphadiazine has advantages similar to those of

sulphathiazole and is, according to Long (1943), less toxic than sulphathiazole. Sodium sulphacetamide (albucid soluble), which has given good results in the prophylaxis of experimental infections, is a highly soluble and diffusible compound (Robson and Tebrich, 1942). When applied in the form of a powder its penetration will be very rapid, but this can be slowed down by making it up in a paste (*e.g.* with glycerine and eucerin) as described by Robson and Wallace (1941) and in *Hospital Treatment of Burns* (1942). Sodium sulphacetamide is also very satisfactory for use as a solution or in an ointment in the conjunctival sac.

Various other compounds of the same type have been suggested and require further investigation. Diamino-diphenyl sulphone has a high chemotherapeutic activity but is relatively toxic. Derivatives can, however, be made which retain the chemotherapeutic activity but are less toxic. Thus Domagk (1942) found that the digalactoside (named Tibatin) is highly effective against hæmolytic streptococcal infections. Domagk has also investigated another compound related to the sulphonamides, namely, the sodium salt of 4-amino-methyl-benzene-sulphonamide (named Marfanil). This compound appears to be highly effective against the organisms of gas gangrene, and its action is not inhibited by para-amino-benzoic acid. It obviously requires further investigation.

Acridine derivatives were used extensively in the last war for the continued treatment of infected wounds. The evidence for their value when applied shortly after infection has already been discussed. It seems well established, however, that when their use is continued under these circumstances for any length of time they tend to interfere with healing. Thus Makins (1922), reviewing the data, concludes that these drugs are opposed to the early development of healthy granulations, and that the process of epithelialisation is slow and inefficient It would seem, therefore, that when the acridines are used in the early stages they should be applied only for a short time, and that the treatment should be continued with another bacteriostatic agent such as a sulphonamide. Proflavine powder, which has been suggested for the treatment of established sepsis, is probably too irritant for use in fresh wounds, and this is supported by the finding of Russel and Falconer (1943) that proflavine powder produces highly destructive changes when applied to various tissues, including muscle and soft tissues.

A most important bacteriostatic agent which has recently become available, at least for experimental purposes, is penicillin. This is a metabolic product of the mould penicillium notatum, and its activity against various organisms, and especially against *Staphylococcus aureus*, was discovered by Fleming in 1929. Florey and his co-workers have been instrumental in developing methods for its production and purification and for clinical investigations. Penicillin is difficult and expensive to make, and until its chemical constitution is elucidated and it can be synthesised, its use will probably remain very limited. Penicillin is one out of a large number of metabolic products elaborated by organisms of various types (moulds, bacteria, etc.), and it seems possible that other substances of equal or even greater importance may ultimately be discovered (see the review by Allcroft, 1942).

Penicillin is more effective than sulphonamides against most pyogenic organisms and, unlike these latter drugs, it is highly active against *Staphylococcus aureus*. It has an extremely low toxicity, lower than that of the sulphonamides, and does not in any way appear to interfere with the natural defences of the body. It also has the great advantage that its activity can be exerted in the presence of pus, which usually produces a marked inhibition of the action of sulphonamides and of the acridines.

Penicillin has the disadvantage that it is very rapidly eliminated from the body, so that when it is given by injection, repeated administrations of large doses are necessary to maintain a bacteriostatic concentration in the body fluids. Thus, for example, Florey and Florey (1943) had to use doses of the order of 15,000 units given intramuscularly every three hours in order to produce adequate effects. On the other hand, it is highly effective when applied locally in quite low concentrations. Thus, Robson and Scott (1943) found that solutions containing only 1 unit per c.c. produced a pronounced bacteriostatic action against experimental *Staphylococcus aureus* lesions, and very striking results were also produced with rather higher concentrations against experimental pneumococcal lesions. Equally striking results have been obtained in experimental lesions produced by various strains of hæmolytic streptococci (Robson and Scott, unpublished observations). So far very few clinical results are available on the use of penicillin in the prevention of sepsis, but the experimental findings suggest that it should prove an agent of the utmost value once it becomes available in sufficient quantities.

sulphathiazole and is, according to Long (1943), less toxic than sulphathiazole. Sodium sulphacetamide (albucid soluble), which has given good results in the prophylaxis of experimental infections, is a highly soluble and diffusible compound (Robson and Tebrich, 1942). When applied in the form of a powder its penetration will be very rapid, but this can be slowed down by making it up in a paste (*e g.* with glycerine and eucerin) as described by Robson and Wallace (1941) and in *Hospital Treatment of Burns* (1942). Sodium sulphacetamide is also very satisfactory for use as a solution or in an ointment in the conjunctival sac.

Various other compounds of the same type have been suggested and require further investigation. Diamino-diphenyl sulphone has a high chemotherapeutic activity but is relatively toxic. Derivatives can, however, be made which retain the chemotherapeutic activity but are less toxic. Thus Domagk (1942) found that the digalactoside (named Tibatin) is highly effective against hæmolytic streptococcal infections. Domagk has also investigated another compound related to the sulphonamides, namely, the sodium salt of 4-amino-methyl-benzene-sulphonamide (named Marfanil). This compound appears to be highly effective against the organisms of gas gangrene, and its action is not inhibited by para-amino-benzoic acid. It obviously requires further investigation.

Acridine derivatives were used extensively in the last war for the continued treatment of infected wounds. The evidence for their value when applied shortly after infection has already been discussed. It seems well established, however, that when their use is continued under these circumstances for any length of time they tend to interfere with healing. Thus Makins (1922), reviewing the data, concludes that these drugs are opposed to the early development of healthy granulations, and that the process of epithelialisation is slow and inefficient. It would seem, therefore, that when the acridines are used in the early stages they should be applied only for a short time, and that the treatment should be continued with another bacteriostatic agent such as a sulphonamide. Proflavine powder, which has been suggested for the treatment of established sepsis, is probably too irritant for use in fresh wounds, and this is supported by the finding of Russel and Falconer (1943) that proflavine powder produces highly destructive changes when applied to various tissues, including muscle and soft tissues.

the number of applications, they appear to have prevented any irritant action. They conclude that "Where staphylococci are the infecting organisms, proflavine has proved more efficient in controlling or eliminating the infection than any other drug or method of treatment." They found the method of value against all the common pyogenic organisms, with the exception of *B. proteus.* The authors state that with the doubtful exception of one case there was no interference with healing. Similar results with proflavine have also been obtained in the treatment of infected granulating burns by Heggie and Heggie (1943)

The action of sulphonamides is markedly interfered with by the presence of pus which contains inhibitory substances, but there is good evidence that they are effective in areas of established infection in the absence of macroscopic pus. Thus, Colebrook and Francis (1941) found that hæmolytic streptococci were frequently rapidly removed from superficial infected wounds by the application of sulphanilamide powder Similarly, Matthews (1942) found that the total number of organisms in infected wounds is markedly reduced by the local application of a sulphonamide, though they are not completely removed. In both these investigations healing appeared to be beneficially influenced. If pus and dead tissue are present in an infected wound it is desirable to use some method of removing these before using the sulphonamide

Penicillin can exert its activity in the presence of pus and should therefore be of great value in the treatment of established infection. Owing to the scarcity of material there are as yet few data available, but they strongly support this opinion Florey and Florey (1943) obtained good results in the elimination of hæmolytic streptococci and staphylococci in infections of the eye and mastoid process and in chronic wound sinuses and other local septic conditions Colebrook and his co-workers (1943) used a penicillin ointment with a lanette wax cod-liver oil base and found this highly effective in removing hæmolytic streptococci and staphylococci from infected burns. The results were better than with propamidine, and healing, on the whole, was more rapid than with propamidine.

The decade of the modern renaissance on anti-bacterial work closed with the publication of results obtained with yet another type of substance. In 1937 King and his co-workers prepared a series of compounds related to synthalin, which had been found effective in the treatment of trypanosomal infections.

Treatment of Established Sepsis

This is the most difficult problem, but modern chemotherapeutic advances are proving of value here too and alternatives to older remedies which will be dealt with first.

Free Chlorine.—Substances releasing free chlorine on contact with the tissues were used very extensively in the last war. The first preparation of hypochlorite was actually introduced in Edinburgh by Lorrain Smith and his co-workers and was named Eusol. Shortly afterwards Dakin introduced a buffered solution of hypochlorite, and this was first investigated by Carrel and Dehelly, who devised a special method of irrigating wounds with it. This was found necessary since the chlorine is rapidly inactivated and fresh supplies of the solution must be brought to the affected areas at repeated intervals. These investigators also introduced quantitative methods for estimating the value of this treatment; careful measurements were made of the rate of healing of the wounds and of their bacterial content at various stages of healing. It was concluded (Makins, 1922) that the method was definitely of benefit, though it is cumbersome and time consuming.

More recently the same principle has been reintroduced with a somewhat different technique. Bunyan (1941) devised the coated silk envelope with which the whole affected area can be surrounded. This rather simplifies the irrigation, and the results so far obtained with hypochlorite solutions suggest that the method may be valuable (see also Vaughan Hudson, 1941). It is as yet not definitely established to what extent the value of hypochlorite is due to a direct antiseptic action of chlorine and to what extent it may be dependent on the clearing away of dead tissue, which undoubtedly occurs. Indeed, Bunyan has suggested that after the pus and dead tissue have been cleared away by hypochlorite, the treatment may be continued with a chemotherapeutic agent A soluble sulphonamide might well prove of value under such circumstances.

Up to recently it seemed established that the acridines were not suitable for long continued treatment, but the matter has been reopened in so far as the treatment of chronic established sepsis is concerned. On the principle of using a powder which will slowly dissolve in the wound, Mitchell and Buttle (1942) used proflavine powder in the treatment of a number of chronic infected wounds. By strictly limiting the total amount used and

Delayed Disinfection —After the stage immediately following infection, complete sterilisation of the wound by a bactericidal substance can no longer be achieved. The multiplication of organisms can, however, be prevented by the use of bacteriostatic substances (sulphonamides, penicillin), and the infection will usually be dealt with by the natural defences of the body.

Established Sepsis —There is evidence that a variety of substances can be effective even at this stage. The chief value of chlorine releasing substances is probably in clearing away dead tissue and pus. Proflavine powder, sulphonamides, penicillin and propamidine appear to exert an action on the infecting organisms, though it is always preferable to remove all purulent material before applying the chemical substance.

It seems likely that with the discovery of new and more active antiseptic and chemotherapeutic substances there will be an appreciable lengthening of the periods during which it will be possible to achieve both immediate and delayed disinfection. A more rapid and effective treatment of established sepsis may also be anticipated.

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These new compounds, the diamidines, were found to be of value in protozoal infections. Later the unexpected finding was made that they are also active against bacteria (Fuller, 1942). One of these compounds, propamidine (4 : 4′-diamino-diphenoxy-propane-dihydrochloride), has been found to have the same effectiveness as sulphathiazole when tested *in vitro* against *Staphylococcus aureus*. Propamidine has the important advantage that its action is not inhibited by pus and tissue fluids. On the other hand, it is of value only when applied locally and not when given systemically.

The margin between the toxic and therapeutic local concentrations of propamidine is much narrower than with the other modern chemotherapeutic agents and hence avoidance of local irritation may prove to a be a serious problem with this drug. A concentration of 0·1 per cent. does not affect leucocytes, but twice this concentration does have some effect, and 0·4 per cent. of the drug may produce necrosis of granulation tissue. 0·1 per cent. is the concentration recommended in the treatment of septic wounds and this does not leave much margin for individual variation. A number of investigators (Thrower and Valentine, 1943; McIndoe and Tilley, 1943, and others) have reported favourable results using 0·1 per cent. of propamidine in a jelly or lanette wax base. It is claimed that infected areas can be cleared of dangerous organisms within ten days and that good healing occurs.

Conclusions

The rapid development in chemotherapy during the last decade has radically altered our conceptions regarding the value of chemical substances in the treatment of infection, though as great an importance as ever is placed on surgical treatment and rest.

The period which follows infection may be roughly divided into three stages and, *ceteris paribus*, it is the stage at which treatment is initiated that largely determines what can be achieved by chemical substances.

Immediate Disinfection.—There is good reason for believing that all the bacteria in an infected wound can be killed by certain substances (*e.g.* some detergents, acridine derivatives) provided that treatment be started very soon after infection. Unless the wound can be closed, however, there is a great danger of re-infection, which can be prevented by the use of a bacteriostatic substance.

REFLEX VASODILATATION IN SURGERY

By J. R. LEARMONTH, Ch M, F.R.C S Ed,
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IN the practical management of many surgical conditions the determining factor is the amount of blood reaching the part. When blood count, blood volume and blood pressure are normal, this is a factor of the sum of the calibres of individual arteries and arterioles. The calibre of these vessels is controlled partly by vasoconstrictor nerves belonging to the autonomic nervous system, and partly by humoral substances, either circulating in the blood (adrenalin), or accumulating locally (products of muscular metabolism). The vessels of the skin and subcutaneous tissue have a regulating mechanism which is predominantly nervous, normally exerted in a positive way by the continuous imposition of vasoconstrictor tone. When these vasoconstrictor impulses are interrupted or inhibited the vessels dilate, and the flow of blood through them increases. On the other hand, the increase of blood-flow demanded by a working muscle is probably provided by the dilating action on its vessels of products of its own metabolism.

A convenient and reasonably accurate method of comparing the amounts of blood flowing through the subcutaneous tissues of an extremity under different conditions is to measure the temperature of the skin of a digit by means of a thermocouple attached to an electrical recording device; the greater the flow of blood the higher will be the temperature. In a healthy young adult, with a normal vascular tree, the temperature of fingers and toes when vasodilatation is fully established is in the neighbourhood of 34° C. More precise values for blood-flow may be obtained by enclosing the part in a plethysmograph, and recently by this method Brown and Allen (1941) have measured in normal subjects increases due to reflex vasodilatation varying from 226 per cent. to 76 per cent., the average increase being 168 per cent. Such large increases in blood-flow can be secured *only when the main* vessels, and their collateral branches, are neither obstructed by organic disease nor held in spasm.

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B. A main artery is plugged by an embolus. Alternative channels which might be adequate are, at least at first, thrown out of commission by intense spasm of reflex origin.

C. A main artery is plugged by a thrombus forming in a damaged segment, for example after arterial contusion. Again the collateral vessels are, at least at first, in a state of spasm

D. A main artery is in a state of spasm, resulting from local irritation of its wall. Here too the spasm may and often does affect the distal collaterals.

Clinical Methods of Improving the Blood-supply to an Extremity

If we leave out of consideration procedures designed to interrupt, temporarily or permanently, the sympathetic vasoconstrictor nerves to a limb, then *heat* emerges as the clinical stimulus effective in producing vasodilatation. It may be applied :—

(1) *To the Affected Part.*—It has been known for many years that the local application of heat is followed by local vasodilatation. This method is probably unobjectionable when the part has an unimpaired blood-supply. Its therapeutic use is to be unreservedly condemned when the nutrition of the part is already precarious, as Sir Thomas Lewis has taught for many years, because " it is quite certain that the warming or heating will increase the metabolism of the tissues and thus increase the blood-flow requirement " (1936). As a result, the part becomes *relatively* ischæmic Examples of the danger of this method of treatment could readily be multiplied : not unusual ones are the rapid appearance and spread of gangrene after the application of hot fomentations to an ulcer on the toe of an arteriosclerotic, and the futility of directly heating under a cage an ischæmic limb threatened by gangrene.

(2) *At a Distance from the Affected Part.*—Thirty years ago Stewart (1911) showed that if the legs or arms were heated, after an interval vasodilatation occurred in the unheated arms or legs. Twenty years later this was confirmed by Landis and Gibbon (1933), who used, as the source of heat, water at from 43° to 45° C ; the vasodilator response became apparent in 15 minutes or so, the skin temperature reaching full vasodilatation level in about 30 minutes (Fig 1) While hot water is the most standard method of providing heat at a distance, it is often inconvenient or impossible to use in clinical practice If a patient is confined to bed, and it is desired

The therapeutic value of an assured supply of blood to a diseased area need not be emphasised, and it should be regarded —as is an operation in total war—as demanding every possible expedient to secure the end. The remainder of this paper deals with the problem of securing a maximal blood-supply in certain surgical conditions involving the extremities, and it is convenient first to consider the pathological basis of these conditions, and second to describe clinical methods of improving the blood supply to an extremity and to narrate one's experience of these methods, successful and unsuccessful.

Pathological Considerations

Two broad groups of lesions can be recognised. There is first a group in which the demand is for a better-than-normal blood-supply. Thus, when a part is infected, it demands an increased supply of blood in order to combat the infecting agent. When a part is wounded, its rapid and stable healing, its defence against simultaneous infection and its chances of controlling infection subsequently introduced all depend upon an increased supply of blood. The histological observations of pathologists have familiarised us with the mechanism (active hyperæmia) by which this need is met; and sometimes—and more often in time of war—surgeons find themselves powerless to deal with the appalling consequences of a breakdown in this mechanism; for example, in cases of injury to the main artery of an extremity, when infection may spread throughout the limb with almost unbelievable rapidity. Then there is a second group, in which the blood-supply to a part has been reduced to a level which makes its continued existence a precarious one, and certainly leaves no available surplus to provide for repair, or for defence against infection. The demand is then for a normal blood-supply. A familiar example is the foot of an arteriosclerotic, pulseless and cold at best, and only too ready to die if called upon to deal with the most trivial injury or infection. Cases belonging to this second group may be subdivided into certain types :—

A. Main arteries, and often collateral channels, are affected by obliterative disease (arteriosclerosis, thromboangiitis obliterans). In many cases the lack of blood is accentuated by spasm of collateral vessels, or by thrombi which form on diseased patches of their walls.

B. A main artery is plugged by an embolus. Alternative channels which might be adequate are, at least at first, thrown out of commission by intense spasm of reflex origin.

C. A main artery is plugged by a thrombus forming in a damaged segment, for example after arterial contusion. Again the collateral vessels are, at least at first, in a state of spasm.

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to increase the blood-flow to the arms, the legs may be heated under an ordinary light cage (Fig. 2); if it is desired to increase the blood-flow to the legs, the forearms and hands may be rested on lockers adjacent to the bed, under cardboard boxes through the roof of which project ordinary electric light bulbs (Fig. 3). Naturally, when the patient is not completely conscious, care must be taken that the directly heated parts are not scorched. Since the vasodilatation is usually accompanied by sweating, during treatment the patient must have plenty of fluids. Under these conditions the whole of the increase in blood-supply becomes available for nutrition, repair, or defence. No part of it is diverted

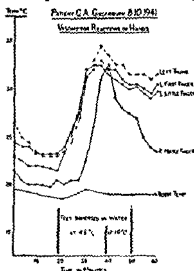


FIG 1.—Typical reflex vasodilatation in the hands, as a result of warming the feet in water at 45° C (Observations by Dr R L Richards)

to provide for increased metabolic requirements. The conditions imposed on the threatened limb should be such that it is not used to heat its environment; to put it in another way, if the endeavour is to preserve the limb, or as much of it as possible, local cooling with its resultant vasoconstriction is to be avoided. However, the parts must be kept dry, to avoid the loss of heat by evaporation of sweat; this is best obtained by the avoidance of dressings, and by regular drying.

The physiology of production of reflex vasodilatation is not simple We may consider in turn —

A. *The Condition of the Vessels in the Part*

It is obvious that, if maximum results are to be secured, the vessels of the part must in fact be capable of dilating, and not



FIG. 2.—Clinical method of warming the feet, to secure reflex vasodilatation in whitlow of a hand; in practice the wire cage is covered by a blanket. (The wide sleeve attached to the overhead bar provides for constant elevation of the hand, while allowing active movement.)



FIG. 3.—Clinical method of warming the hand(s), to secure reflex vasodilatation of the feet, for example in threatened gangrene of a toe.

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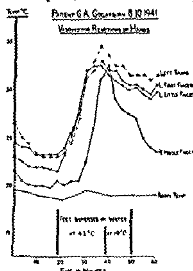


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reserve is the effect of a local lesion of the main artery, whether caused by injury (arterial contusion) or disease (thrombosis, embolism). We owe to Leriche (1939) the recognition of the spasm, temporary or permanent, imposed on collateral vessels by the presence of such a lesion. We must also remember that while a local injury, or a small embolus, may not obstruct the mouths of many collateral vessels, a thrombus may be so placed that it cuts off the blood-flow into many branches. If the diseased or injured part of the artery be cleanly removed, it may be possible to dilate the remaining channels by the reflex method; but as these patients are older, and the collaterals less resilient and possibly reduced in number, the success of the procedure may be apparent only in the provision of a normal, or nearly normal flow of blood, that is to say, in these circumstances it may be impossible to demonstrate any dramatic increase in skin temperature.

Arterial Injury.—A cheerful hypertensive blacksmith, aged 70, was admitted to my wards in the Royal Infirmary with the story that, while he was wielding a heavy hammer, a chip of steel had struck his left leg, behind the knee. The leg and foot were cold, powerless and pulseless.* At operation it was found that the splinter had divided the popliteal artery at its bifurcation. The vessel was cleanly tied, and the patient returned to bed, with heat to his trunk and arms At first it seemed as if he must lose his leg, but soon the circulation was restored. Three days afterwards the temperatures of his legs were as shown in Fig. 5. It is now more than a year since his accident; the other day I sent for him, for the purpose of this lecture; he could spare me a little time on a Sunday, for he is swinging his hammer for twelve hours daily I am sure that if we had heated his leg directly, he would have lost it

Arterial Thrombosis.—An aircraftsman from the Middle East, aged 35, was kindly referred to me by Air-Commodore Cade. He had pain in the sole of his left foot, his dorsalis pedis and posterior tibial pulses were absent, and there was a trophic ulcer under his 5th metatarso-phalangeal joint. As will be seen (Fig. 6), reflex vasodilatation was normal in his right foot, but absent in his left. An arteriogram showed that about 12 cm. of his femoral artery were obliterated by a thrombus, which blocked the openings of many anastomotic arteries In this case the collateral circulation

* I am indebted to my colleague, Mr T McW. Millar, who saw the patient on admission, for acquainting me at once with the state of affairs

was doing nearly its best: the circulation did not improve after distant heating. However, a left sympathectomy was followed by

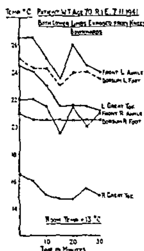


FIG 5—Skin temperatures of feet and legs, exposed to a room temperature of 13° C, 3 days after ligation of severed left popliteal artery. The superficial circulation in the foot on the injured side is actually better than that on the normal side. (Observations by Dr R. L Richards)

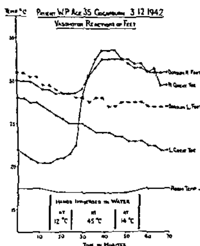


FIG. 6—Reflex vasomotor responses in feet of patient with thrombosis of left femoral artery. On the right side the response is normal, on the left it is absent, the foot gradually cooling towards room temperature. (Observations by Dr R L Richards)

a rise of 2° C., showing that the collateral vessels had not been fully utilised, as a consequence of vasoconstriction imposed by the

reserve is the effect of a local lesion of the main artery, whether caused by injury (arterial contusion) or disease (thrombosis, embolism). We owe to Leriche (1939) the recognition of the spasm, temporary or permanent, imposed on collateral vessels by the presence of such a lesion. We must also remember that while a local injury, or a small embolus, may not obstruct the mouths of many collateral vessels, a thrombus may be so placed that it cuts off the blood-flow into many branches. If the diseased or injured part of the artery be cleanly removed, it may be possible to dilate the remaining channels by the reflex method; but as these patients are older, and the collaterals less resilient and possibly reduced in number, the success of the procedure may be apparent only in the provision of a normal, or nearly normal flow of blood; that is to say, in these circumstances it may be impossible to demonstrate any dramatic increase in skin temperature.

Arterial Injury.—A cheerful hypertensive blacksmith, aged 70, was admitted to my wards in the Royal Infirmary with the story that, while he was wielding a heavy hammer, a chip of steel had struck his left leg, behind the knee. The leg and foot were cold, powerless and pulseless.* At operation it was found that the splinter had divided the popliteal artery at its bifurcation. The vessel was cleanly tied, and the patient returned to bed, with heat to his trunk and arms. At first it seemed as if he must lose his leg, but soon the circulation was restored. Three days afterwards the temperatures of his legs were as shown in Fig. 5. It is now more than a year since his accident; the other day I sent for him, for the purpose of this lecture; he could spare me a little time on a Sunday, for he is swinging his hammer for twelve hours daily. I am sure that if we had heated his leg directly, he would have lost it

Arterial Thrombosis—An aircraftsman from the Middle East, aged 35, was kindly referred to me by Air-Commodore Cade. He had pain in the sole of his left foot, his dorsalis pedis and posterior tibial pulses were absent, and there was a trophic ulcer under his 5th metatarso-phalangeal joint. As will be seen (Fig. 6), reflex vasodilatation was normal in his right foot, but absent in his left. An arteriogram showed that about 12 cm. of his femoral artery were obliterated by a thrombus, which blocked the openings of many anastomotic arteries In this case the collateral circulation

* I am indebted to my colleague, Mr T. McW. Millar, who saw the patient on admission, for acquainting me at once with the state of affairs

measures, with sufficient, if occasional, success to justify their continuance. I have not obtained the precise information which only an arteriogram can afford, but the assumption is that when conservative methods are successful the disease has a patchy distribution, and some at least of alternative vascular channels can be dilated and put into service. Recently, de Takáts and Miller (1942) have had similar encouraging results, and have given precise figures for the increases of blood-flow so obtained. One can hope to increase the blood-flow in such cases only from "precarious" or "very poor" to "poor"; but that may be enough to avoid an artificial limb or crutch. One example will suffice:—

A man aged 67 was admitted to the Western General Hospital,

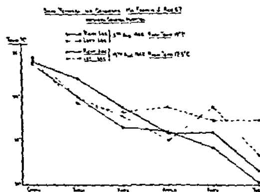


Fig 8—Temperature gradients in legs of patient with threatened arteriosclerotic gangrene of left foot, showing improvement in skin temperatures after two weeks of treatment by reflex vasodilatation (Observations by Dr R. L. Richards)

with a swollen dusky left great toe. Popliteal, posterior tibial and dorsalis pedis pulses were absent, and the foot felt cold. The temperature gradient in the legs is shown in Fig. 8. An attempt was made to improve the circulation in the feet by heating the arms, and this was rapidly successful. The improvement is shown graphically in Fig. 8, and in 6 weeks the patient walked out of hospital. I quite realise that other factors—rest, diet, etc—may have contributed to such a result, but my colleagues in hospital also emphasise the value of treatment by reflex vasodilatation.

B. *The Condition of the Nerves to the Part*

Reflex vasodilatation in extremities is dependent on the integrity of their vasoconstrictor nerves, dilatation follows the inhibition of normal vasoconstrictor tonus

diseased segment. This has now been resected, and the nutrition of the limb is completely adequate.

Arterial Embolism.—A lady aged 48, suffering from auricular fibrillation, was admitted to Dr A. Rae Gilchrist's wards with embolism of the left popliteal artery. I agreed with Dr Gilchrist that the interval since lodgement of the embolus—18 hours—was too long to justify its surgical removal, and the patient was treated by heat to her trunk and arms. Eight days later an embolus lodged in her right femoral artery, and was removed after 6 hours, under local anæsthesia, with immediate restoration of circulation in the

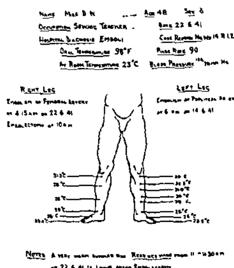


Fig. 7.—Case of embolism of both femoral arteries Comparative readings on right side (after embolectomy) and on left side (conservative treatment by reflex vasodilatation). (Observations by Dr R. L. Richards.)

limb. An hour after embolectomy we were able to compare the blood-flow on the two sides; it can be seen (Fig. 7) that there is no marked difference between them Unfortunately further multiple emboli subsequently led to the death of this patient.

Generalised Arterial Disease.—It seems illogical to employ reflex vasodilatation in an attempt to improve the nutrition of the feet and legs of elderly arteriosclerotics, and indeed in many cases I have failed to do so, and have been forced to amputation. However, I have a distinct impression that these nutritional lesions are more common just now, possibly because present conditions of life bear hardly on elderly people; I see a good many examples in hospitals and, unless gangrene is established, I usually attempt to improve the circulation at least temporarily by conservative

measures, with sufficient, if occasional, success to justify their continuance. I have not obtained the precise information which only an arteriogram can afford, but the assumption is that when conservative methods are successful the disease has a patchy distribution, and some at least of alternative vascular channels can be dilated and put into service. Recently, de Takáts and Miller (1942) have had similar encouraging results, and have given precise figures for the increases of blood-flow so obtained. One can hope to increase the blood-flow in such cases only from "precarious" or "very poor" to "poor"; but that may be enough to avoid an artificial limb or crutch. One example will suffice:—

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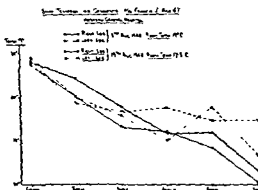


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B. *The Condition of the Nerves to the Part*

Reflex vasodilatation in extremities is dependent on the integrity of their vasoconstrictor nerves, dilatation follows the inhibition of normal vasoconstrictor tonus.

It is therefore impossible reflexly to increase the temperature of a sympathectomised limb by applying heat to the other extremities. *Moreover, it has been shown, both by dissection and* by clinical observation, that at least in the hands and feet the final distribution of vasoconstrictor nerves corresponds to that of the cutaneous nerves; the arrangement in the arm is shown in Fig. 9, which is constructed from the original figures of Kramer and Todd (1914). Thus reflex vasodilatation cannot be produced in the territory of a divided peripheral nerve; and though the responses are on occasion not quite clear-cut, it is extraordinary

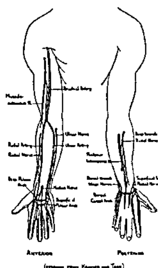


FIG. 9.—Distribution of nerves to blood vessels of upper extremity: redrawn from the data of Kramer and Todd

how sharply they may be defined. Incidentally, this is unfortunate, because obviously the method cannot be used in the treatment of the ulcers so often seen in anæsthetic areas, in patients suffering from lesions of peripheral nerves. There is a further disappointment in war-time, that the method fails in the very cases when its success would be most welcome, when there has been injury to both the main vessel and to the nerves of a limb. On the other hand, damage to an artery may impair collateral circulation, even when the nerves of the limb have been severed.

A boy of 9 was kindly referred to me at Gogarburn Emergency Medical Service Hospital by Mr C. Charleson of Perth. The previous evening he had been wounded in the right axilla by a splinter from a chance-found military grenade, a large gap being

present in the anterior axillary fold, and the humerus fractured. The arm was cold and powerless, although at first the radial pulse could just be felt. Mr Charleson had rapidly excised the wound —which incidentally remained bacteriologically clean—and had put the arm in a brachio-thoracic plaster. He consulted me by telephone about its nutrition: the wound was so large that it was difficult to apportion the deficit between vascular and nervous damage. As it transpired, quite unhelpfully I advised reflex vasodilatation. Twenty-four hours later, when I saw the boy, the hand was cold and pulseless, and quite unresponsive to warming of the trunk and limbs. After removal of the plaster (which did not improve the condition of the circulation), I re-explored the wound, and found that the axillary artery was now thrombosed. The injured length of vessel was resected: and within a minute we could see, and appreciate by touch, the restoration of the circulation to the hand Subsequent examination and exploration showed that the musculo-cutaneous, median, and radial nerves were divided, and that the ulnar nerve, though not divided, was so bruised that it did not conduct

In such complicated injuries it seems to me that at least in childhood, youth and young adulthood, when the patient is very ill, and there is doubt as to the exact pathological lesion, absence of improvement after adequate attempts at reflex vasodilatation should lead to the early exploration or re-exploration of the wound, and particularly of the main artery Cohen (1940-41), in a valuable and critical paper, and Jones (1939) have expressed the same view.

It is also important to remember, when operating on such cases, that even when the sympathetic nerves to a limb have been interrupted, arteries resent rough handling, and may register their protest by going into intense spasm at the site of the operative insult

Thus while operating on a femoral artery under spinal anæsthesia (which interrupts vasoconstrictor fibres as they leave the spinal cord in the anterior roots), during a difficult exposure we have seen the artery become so narrow that the distal pulses disappeared, and the subsequent arteriogram was almost valueless

These matters are all concerned with the efferent part of the reflex pathway Observations on the afferent path have been made by Duthie and Mackay (1940) These observers found that reflex vasodilatation could be elicited by heating a limb in which thermal sensation was absent thus, after unilateral cordotomy,

It is therefore impossible reflexly to increase the temperature of a sympathectomised limb by applying heat to the other extremities. Moreover, it has been shown, both by dissection and by clinical observation, that at least in the hands and feet the final distribution of vasoconstrictor nerves corresponds to that of the cutaneous nerves; the arrangement in the arm is shown in Fig. 9, which is constructed from the original figures of Kramer and Todd (1914). Thus reflex vasodilatation cannot be produced in the territory of a divided peripheral nerve; and though the responses are on occasion not quite clear-cut, it is extraordinary

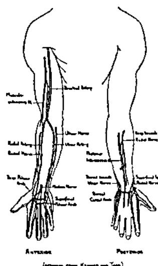


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and the interruption of intraspinal autonomic neurones after thrombosis of the posterior inferior cerebellar artery, evidence is lacking of vasomotor autonomy in the ganglia of the sympathetic chains.

Consideration of these clinical data suggests that reflex vasodilatation does not depend upon the integrity of the nerve supply to the heated part, but may be brought about as a result of heating the blood passing through it. The autonomic centres in the hypothalamus are sensitive to changes in the temperature of the blood, and when this is increased they arrange for the release of vasoconstrictor tonus throughout the body. This hypothesis is in keeping with the latent interval before the reflex appears, and with the rapidity with which it reaches its maximum. However, Duthie and Mackay (1940) have been able to record reflex vasodilatation, when the heated extremity had had its circulation completely occluded by the cuff of a sphygmomanometer; in these circumstances the heated blood could not reach the hypothalamus. Here at the moment the matter rests, but no doubt further clinical experience will discover the nature of the mechanism—or mechanisms—concerned in the reflex

I have attempted to weave into the more theoretical part of this lecture examples—some successful, some unsuccessful—of the clinical application of the production of reflex vasodilatation. It will possibly be of advantage if I now try to draw together the points of practical importance, and add to the conditions I have enumerated certain others in which my colleagues and I have found the method of value.

(1) *In Organic Peripheral Vascular Disease*.—The method is worth a trial: in cases in which gangrene is threatened, but not established, and after limited ablation of gangrenous tissue It has been claimed that local ischæmia is of itself an adequate stimulus to promote local vasodilatation, a short experience of such cases will show that this view is inaccurate

(2) *In Embolism of a Main Artery*.—To ensure that, after the spasm of collateral vessels has disappeared, the acral circulation will be maximal

(3) *In Aneurysm*.—To tide over temporary circulatory deficiency. Operations on aneurysms of the extremities should be preceded by sympathectomy.

(4) *In Pyogenic Infective Conditions of the Hand or Foot*.—It may be argued that the fever which is usually present in such conditions is invariably accompanied by vasodilatation That is

heating of the thermanæsthetic leg will produce full vasodilatation in an arm; and after thrombosis of the posterior inferior cerebellar artery, which is followed by thermanæsthesia on the opposite side, heating of an arm or leg on the thermanæsthetic side will be followed by vasodilatation in the remaining limbs. In the Nerve Injuries Unit at Gogarburn we have found that reflex vasodilatation may be produced in the other extremities by heating a completely anæsthetic area of a limb. Thus, in total lesions of a brachial plexus, the reflex may be produced in the unaffected extremities by heating the insensitive digits and hand.

Clinical experience seems to show that, for a time at least, the presence of a local arterial lesion will prevent the production of reflex vasodilatation in the affected limb. It is easy enough to understand this when there has been simultaneous injury to the nerves which carry vasoconstrictor fibres, as in one of the cases I have described It is less easy to understand when the innervation of the limb is intact. A number of cases have been recorded of arterial spasm proved at operation, and treated conservatively by attempts to produce reflex vasodilatation. In those I have scrutinised, when the progress of the patient has been recorded in sufficient detail, improvement in the distal circulation has always shown a time-lag, beyond the interval one is accustomed to see between the application of heat and the appearance of reflex vasodilatation, in such circumstances it is possibly doubtful if the method is of direct efficacy in relaxing the spasm, although its clinical employment on other and obvious grounds is to be encouraged. It is known that the continuance of the spasm is not dependent on afferent impulses traversing the nervous network in the adventitial coat of the vessel, because—as in Mr Murray's case—neither the subadventitial injection of novocain nor the performance of a periarterial sympathectomy proximal to the spasm will restore the circulation after an interval shorter than those that have characterised cases in which apparently spontaneous recovery has taken place Yet it is undoubtedly possible, as I have described, for a thrombosed segment of artery to impose spasm on its collateral circulation when the limb is denervated. To explain this, it is attractive to search for reflex pathways constructed in short relays Work on this complex subject is proceeding but one can start from the assumption that, if present, these pathways are peripheral to both intraspinal mechanisms and to the sympathetic ganglia, because after the interruption of preganglionic neurones by operation,

and the interruption of intraspinal autonomic neurones after thrombosis of the posterior inferior cerebellar artery, evidence is lacking of vasomotor autonomy in the ganglia of the sympathetic chains.

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so: but after drainage, and during the stage of resolution and repair when fever is absent, I am convinced that the provision of a better-than-normal blood-supply makes for sounder healing and better function.

(5) *In Ulceration.*—Ulcers of the extremities, especially when acral, respond very favourably to the enforced better-than-normal blood-supply which can be provided by reflex vasodilatation.

(6) *In Skin-grafting.*—When a skin graft must be applied to an extremity, and especially to the distal part of the extremity, it need not be emphasised that the host area should have the maximal possible blood-supply, especially during the period when the graft is "taking." I have no personal experience of such cases: but my colleague Mr A. B. Wallace has given me particulars of 13 cases in which he has employed the method in plastic procedures upon the hands or feet. For the period under review these cases represented 8.7 per cent. of the total number of patients admitted to his unit. He is convinced of the efficacy of the procedure.

(7) *In Musculo-tendinous Lesions.*—When the repair of tendons must be undertaken in a hand often robbed of direct blood-supply by the original accident, the local blood-supply may be improved by this procedure. But it has very definite limitations: for when a condition akin to ischæmic contracture has supervened on an injury to the brachial artery of a healthy young adult (and such cases are within the knowledge of those interested), in my experience the method has nothing to offer; even although, by some unexplained vagary of arterial blood-supply, certain muscles may have emerged relatively unscathed from the vascular famine. I believe that a similar situation may be encountered in the lower extremity, but evidence for this is as yet incomplete.

I have had some hesitation in presenting these problems in a Honyman Gillespie lecture, because the attempt at their solution has not been a wholly personal task. However, the objects of this lecture have been twofold: to draw your attention to a useful clinical procedure, and to emphasise the importance of extracting from every clinical case as much information as possible towards the solution of certain problems in hominal physiology. For assistance in the second object I desire to thank all those, whose names I have mentioned, who have been good enough to refer to me for investigation or operation patients suffering from conditions in which they were aware of my interest: and especially

Dr R. L. Richards, now working with a personal grant from the Medical Research Council, for his painstaking observations on the vasomotor phenomena.

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Structure and Relations of the Pouch

The pouch is composed of mucosa, submucosa and a fascial covering of varying thickness derived from the pharyngeal aponeurosis. It is formed by a true herniation, and no muscle tissue, therefore, is found in the wall, although a few fibres have occasionally been observed in small pouches. Well-developed muscle fibres surround the neck of the sac.

The situation of the pouch is determined by the arrangement of the fibres of the inferior constrictor muscle. The lower portion of the muscle, which has its origin in the cricoid cartilage, is usually referred to by laryngologists as the crico-pharyngeus, and can be differentiated into two parts. The lower fibres pass

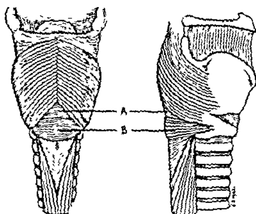


FIG 1—A, Site of origin of pouch between oblique and transverse fibres of crico-pharyngeus, B, Crico-pharyngeal sphincter

transversely from side to side and form the crico-pharyngeal sphincter, while the upper fibres pass obliquely with an inclination upwards to join the median raphé on the posterior pharyngeal wall The opening of the diverticulum is invariably situated posteriorly in or near the midline in the potentially weak area between the oblique and transverse fibres of the crico-pharyngeus (Fig 1)

By the time symptoms are present the pouch is usually of appreciable size The smaller pouches are globular in shape and project backwards and downwards for a short distance. The larger sacs are more often pear-shaped, and extend down behind the œsophagus, the fundus frequently reaching the level of the thoracic inlet, and in some cases even extending into the posterior

THE SURGERY OF THE HYPOPHARYNX: PHARYNGEAL POUCH

By J. M. GRAHAM, M.B., Ch.M., F.R.C.S.Ed.
Surgeon, Royal Infirmary, Edinburgh

PHARYNGEAL diverticulum and post-cricoid carcinoma are the surgical affections of the hypopharynx which merit special consideration, and I propose to discuss these conditions, basing my observations mainly on the cases which have been under my own care.

The term hypopharynx is sometimes used to indicate the whole of the laryngo-pharynx, but it seems preferable to employ it in a more restricted sense to indicate the narrow lower end of the pharynx which lies behind the cricoid cartilage.

Pharyngeal diverticulum is a much less common condition than malignant disease of the hypopharynx. Both congenital and acquired types of diverticulum are found in relation to the pharynx. The congenital varieties, which will not be referred to further, are rare developmental sacs whose origin can be traced to the second, third and fourth branchial pouches. They consist usually of a cystic dilatation communicating through a narrow track with an opening situated in relation to the tonsillar fossa, pyriform sinus or lateral wall of the pharynx. A rare form of pouch has also been observed by Hurst, situated in the midline behind the larynx and lying in front of the œsophagus.

The Acquired Form of Pharyngeal Diverticulum

This is the more common and important variety of diverticulum of the pharynx It is frequently referred to as a pressure or pulsion type of diverticulum. Until comparatively recent times it was usually described as a diverticulum of the œsophagus, and even to-day apparently not all of those who refer to the subject are clear on the essential facts, although these have long been established.

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however, is present, as an instrument is easily passed into the œsophagus after the pouch has been freed and displaced upwards at operation.

Etiology

There is no evidence that the common pharyngeal type of diverticulum is congenital in origin. Like the direct type of hernia in the inguinal region, it is due to stretching and yielding of the muscular wall at an area which is potentially weak. The fact that the herniation occurs above the crico-pharyngeal sphincter and not in the posterior wall of the œsophagus immediately below, where the gullet is weakened by the absence of the longitudinal muscular coat, suggests that spasm or failure of relaxation of the sphincter may play an important part in the etiology. The not infrequent long history of slight difficulty in swallowing, sometimes dating back to youth, is suggestive of inco-ordinate action of the sphincter. It can readily be understood how slight resistance to the passage of food, by raising the intrapharyngeal pressure during the act of swallowing, would favour the formation of a pouch. The observation that the passage of a bougie in early cases of pharyngeal pouch may temporarily relieve the symptoms of dysphagia supports the view that abnormal sphincteric action is an important factor. This impression is confirmed by the recorded fact that the slight dysphagia which has persisted in certain cases after removal of the pouch has been relieved by dilatation.

Recently I have had the opportunity of seeing a case under the care of Professor Davidson which provides evidence in support of the part played by the sphincter. The patient, a woman of fifty-nine, with a pouch of moderate size, has had for over a year comparatively slight difficulty in swallowing, although on certain occasions in the past, when she was particularly worried, the dysphagia had been complete for several days at a time.

Another case, a man of sixty-three, with a small pouch, has been almost completely free from symptoms for several years, although when first seen six years ago he had marked difficulty in swallowing.

The intermittent nature of the dysphagia in these cases indicates spasm or failure of relaxation of the sphincter. It is probable that increased resistance on the part of the pharyngeal sphincter and progressive weakness of the pharyngeal wall with advancing years both share in the production of the diverticulum.

mediastinum as far as the arch of the aorta (Fig. 2 (*a* and *b*)). The pouch may project slightly more to one side than the other, with an inclination usually towards the left. In an exceptional case which I observed a large double pouch was present. The two divisions were equal in size, and each communicated with the pharynx through a large opening lateral to the median plane. It appeared in this case that the herniation had occurred at the usual level, but that the central part of the weak area had proved to be more resistant to pressure from within.



FIG. 2.—(*a*) Large pouch extending down to the arch of the aorta; (*b*) Shows position of pouch in posterior mediastinum.

The opening into the pouch is at first placed on a vertical plane on the posterior pharyngeal wall, but gradually it becomes horizontal as the pouch increases in size and is dragged downwards by the weight of its contents into line with the pharynx above. Except in the case of very small pouches, the opening is usually comparatively large, and the ordinary œsophagoscope passes through it easily. As the pouch enlarges downwards, the œsophageal opening becomes displaced forwards and appears as a narrow, closed slit at the anterior aspect of the neck of the sac. The altered position of the upper opening of the œsophagus explains the difficulty found in passing a bougie or an œsophagoscope, and is no doubt responsible for the marked degree of dysphagia in the later phases of some cases. No actual stenosis,

was not borne out by the results. Only one patient, a woman of fifty-nine, was obviously anæmic.

All the patients complained of some difficulty in swallowing and of a tendency to regurgitation of food, while some were also worried by the unusual sounds which accompanied deglutition. None of the patients had suffered pain.

The severity of the symptoms is usually but not always in proportion to the size of the pouch and tends to increase with time; but there are exceptions to this also, and mention has already been made of two patients who suffer less inconvenience now than they did formerly.

Duration of Symptoms.—The usual history is of slight and indefinite symptoms at first, with gradual appearance of the more troublesome features. The characteristic symptoms, however, develop sooner in some patients than in others In 5 of my cases the symptoms had existed for from five to thirty years, and in the remaining 5 for from one to two years. Two of the patients, both over seventy years of age, with a history of definite symptoms for twenty and thirty years respectively, had noticed a slight abnormality in swallowing since early youth.

Dysphagia—Solid foods, and particularly meat and fruit, are most likely to cause trouble, but there may be difficulty also with fluids. The dysphagia may be quite obvious to the patient, who complains that solid food is apt to stick or can be made to pass down only after repeated gulpings or by drinking water. On the other hand, it may be inferred from the fact that the patient has to take his food slowly or cannot swallow more than a limited amount of water at a time without tending to choke. With care the patient so inconvenienced may succeed in taking an almost normal diet. In only one case had the dysphagia increased to such an extent that the patient continued to lose weight, finally being reduced to a condition of complete starvation.

Gurgling Noises.—Involuntary noises when swallowing were complained of by all but two of the patients, and gurgling sounds were noted in one of the latter when observed drinking water. In two of the cases the chief complaint was of the unpleasant sounds which accompanied every meal, and on this account both patients were unwilling to eat in public. The sound produced in one case was a high-pitched, squeaking gurgle which could be heard at a considerable distance.

Regurgitation.—This symptom was noted at some time in every case, although the frequency varied greatly, the regurgita-

If deranged sphincteric action is the only constant factor, it is remarkable to find pharyngeal pouch so much commoner in males than in females, considering that the spasmodic type of dysphagia at the upper end of the œsophagus is confined almost entirely to women. It should also be noted that some patients are completely relieved of dysphagia after the fundus of the sac has been anchored at a higher level in the neck. It is likely, therefore, that the element of spasm is not always the only or the important factor in the etiology, and that the herniation is due in some cases mainly to the weakness of the pharyngeal wall. The significance of the sphincter and of acquired weakness in the pharyngeal wall as the main factors in the etiology of pharyngeal diverticulum probably varies in the individual case

Observations on Ten Cases of Pharyngeal Diverticulum

Although the number of cases observed may appear to be small, it must be remembered that the condition is not very common. During the period of eleven years from 1930 to 1940 inclusive, only 18 cases with a diagnosis of pharyngeal diverticulum were admitted to the various departments of the Edinburgh Royal Infirmary. As the diagnosis is sometimes unduly delayed or missed in practice, it may be useful to draw attention to the principal features of a condition which frequently causes the patient a considerable degree of inconvenience and distress, and which ultimately may have serious consequences. The cases under review illustrate most of the main points of the condition as well as the problems which arise in regard to treatment.

Clinical Features and Symptoms.—In the series of 10 cases, eight of the patients were males and two were females. All the recorded series show a preponderance of males over females, which may be stated on the average to be in the proportion of 4·5 to 1

Pharyngeal diverticulum characteristically occurs in middle-aged and elderly patients. In my own cases the ages were 76, 73, 72, 67, 63, 60, 59, 56, 50 and 31, the last being one of the youngest patients on record.

With the exception of one male who weighed 14 stones, all the patients were thin and underweight. The general condition of most of them proved to be surprisingly good, and, although the age and loss of weight in certain of the cases suggested that they were poor subjects for a major operation, this impression

at night to 100°. The cause of the pyrexia was not apparent and gave considerable anxiety to his physicians before, by exclusion, it was decided that the source of infection was probably the pouch. In these two cases the symptoms due to mild respiratory infection did not recur after operation.

Diagnosis.—There are few surgical conditions which can be diagnosed so simply and with such certainty. In most cases the history and symptoms point to the diagnosis The pouch can be demonstrated in every case by an X-ray examination after an opaque meal. Under the screen the barium is seen to fill the pouch before it enters the œsophagus. There is no difficulty, therefore, in differentiating the condition from dysphagia due to a simple or malignant stricture or associated with the Plummer-Vinson syndrome. An œsophagoscopic examination can only confirm the diagnosis, but is of value in giving additional information regarding the exact site and size of the opening into the diverticulum.

Prognosis.—The presence of a pouch may ultimately shorten the patient's life. There are numerous records in the literature of patients who have died from starvation or from respiratory infection. Inflammation of the mucosal lining has, in exceptional cases, led to cellulitis in the neck or mediastinum. Malignant disease in the form of an epithelioma may develop in the mucosa as a result of long-standing irritation, and this was observed in one of my cases. Zenker reported that of 27 cases of pharyngeal diverticulum observed post mortem, 13 had died from some complication due to the presence of the pouch.

Palliative Treatment.—In early cases where the pouch is small, occasional dilatation is said to give relief, but the passage of a bougie is rarely easy and may be dangerous.

Cases are recorded in which the patients have obtained considerable relief, when regurgitation was a troublesome feature, by emptying the pouch after meals and before going to bed. The pouch can be washed out if the patient drinks some water and applies pressure over the neck with the head bent low, repeating the procedure several times. The method employed by the celebrated Lord Jeffrey, who used a specially designed spoon to empty his pouch, appears to be unique

Palliative treatment is, however, a poor substitute for radical operation.

Surgical Treatment.—The early results recorded after excision of the sac showed a considerable mortality from infection of the

tion occurring in certain patients only at rare intervals and in others accompanying every meal. Most patients have from time to time to cough up mucus or saliva which has collected in the pouch. In some cases actual regurgitation is prevented by repeated gulpings and re-swallowing. The return of undigested food a considerable time after a meal marks the characteristic phase of regurgitation, and is especially liable to occur spontaneously when the patient bends forwards or is recumbent.

Swelling in the Neck.—An obvious swelling, taking the form of a fullness beneath and behind the sternomastoid muscle in the lower part of the neck, was observed when the pouch was full in four of the cases. In three patients it was situated on the left side, but in the fourth case—a man with a large double pouch—it could be observed on both sides. The swelling can be reduced in size by pressure, and this is usually accompanied by gurgling noises. Some of the patients had learned to empty the pouch in this way.

Coughing and Choking Attacks.—There is a tendency for the contents of the pouch to overflow into the larynx. The frequency and severity of this feature, however, vary greatly in individual cases. Three of the patients, whose symptoms were typical, did not suffer in this way at all. One other patient complained of a choking sensation when the food was retained in the pharynx, and of a temporary hoarseness, but the irritation of the larynx went no further. One man suffered for years from severe attacks of coughing which only came on at night shortly after lying down, while another suffered just as constantly, but always in the morning, while taking porridge. As regurgitation occurred only at a later period in the latter case, the cause of the coughing was not suspected for several years. Still another patient was aware that food tended to go the wrong way, but, knowing his limitations, he seldom took more than a small amount at a time, and rarely had a choking attack.

Respiratory Infection.—Overflow of the contents of the pouch into the larynx, especially at night, may also be the cause of a respiratory infection, the origin of which is easily overlooked. One elderly patient had suffered from repeated attacks of mild bronchitis with a temperature ranging from 100° to 101°, and on medical advice had sought relief by wintering in Egypt for several years, without avail. A second patient, aged seventy-three, who was known to have a pouch, suffered for several weeks from an ill-defined, debilitating illness with a temperature rising

at night to 100°. The cause of the pyrexia was not apparent and gave considerable anxiety to his physicians before, by exclusion, it was decided that the source of infection was probably the pouch. In these two cases the symptoms due to mild respiratory infection did not recur after operation.

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cellular spaces of the neck and mediastinum. There has been ample evidence in recent years to prove that the risks of operation can now be reduced to a minimum. The safety of the modern operation can be attributed to improvements in aseptic technique and in anæsthesia, and also to the introduction of modifications in the operation contributed by various surgeons.

Types of Operation.—The surgeon has the choice of three procedures. He can resect the pouch in one or two stages, or may choose in certain cases the more conservative operation of diverticulopexy. At the present day the two-stage method is followed by the majority of surgeons, but there are others equally experienced who prefer to resect the pouch in one stage, or who perform a two-stage operation only in the case of the larger pouches. The operation of diverticulopexy, which was described by Hill in 1918, has a more limited scope, and is indicated only in the case of frail and elderly patients whose symptoms demand surgical relief with the minimum of risk.

Four of the cases in this series were operated on by the two-stage method, and in four cases the operation of diverticulopexy was performed. The symptoms in the remaining two cases were comparatively slight, and operation has not yet been considered necessary

Preliminary Treatment —When the patient is undernourished and dehydrated, saline and glucose by the intravenous drip method are given for one or more days before operation. A longer preparation is necessary if the patient is suffering from starvation. Most authorities prefer to feed the patient through an œsophageal tube introduced by a laryngologist or guided by a thread. In one of my cases it was necessary to perform a gastrostomy, and to postpone the operation on the pouch for two weeks.

Before the operation the pouch should be emptied by pressure after the patient has swallowed some mild antiseptic. Large pouches may require to be emptied by suction through an œsophagoscope.

Anæsthesia —Intratracheal anæsthesia with gas and oxygen or ether has proved satisfactory in all of my cases. Some surgeons prefer local anæsthesia by regional block of the cervical plexus on both sides

Exposure of the Sac.—The exposure and dissection of the sac are similar in all three procedures

The incision is made, unless the pouch lies more to the right, on the left side along the anterior border of the sternomastoid

muscle from the level of the hyoid bone to a point immediately above the medial end of the clavicle. The omohyoid muscle is divided, and the sternomastoid and carotid sheath with its contents are retracted laterally. After division and ligation of the middle thyroid vein the lateral lobe of the thyroid is freed and pulled anteriorly. The inferior thyroid artery may require to be ligated and divided. The lateral edge of the sac is seen after the pretracheal fascia has been divided. When the sac is small it may not at once be obvious, but it can always be located by the passage of a stomach tube, which invariably enters the pouch. The separation upwards of the pouch from the back of the œsophagus is usually accomplished without difficulty, the most important point of the dissection being at the neck of the sac, which must be thoroughly freed from the connective tissue binding it to the œsophagus (Fig. 3). Lahey particularly has emphasised the importance of this dissection and of freeing the far side of the neck of the sac, which can be done by gentle traction on the pouch and rotation of the œsophagus. Some of the sphincteric fibres are usually divided in clearing the lower aspect of the neck of the sac. Care must be taken not to wound the junction of the pouch with the pharynx, and to avoid injuring the recurrent laryngeal nerves. After the pouch has been carefully freed and held upwards, a stomach tube can easily be passed into the œsophagus.

Diverticulopexy.—When the patient is regarded as a bad surgical risk, the operation is completed by anchoring the pouch in an inverted position The fundus is fixed by several fine silk sutures to the prethyroid muscles in a position which will maintain it at as high a level as possible above the opening in the pharynx without undue tension (see Fig 6*b*). A strip of dental rubber is left in the space formerly occupied by the pouch.

One-stage Resection.—After the sac has been removed the neck is closed by suture, by transfixion and ligation, or by a modified cuff technique which leaves a redundant portion of the fascial coat to be sutured over the mucosal stump Care must be taken to avoid the risk of encroaching on the pharyngeal mucosa by undue traction

Two-stage Resection.—The first stage is completed by fixation of the pouch high in the neck, as described in the operation for diverticulopexy. If the pouch is larger than usual it is stitched to the skin edges at the upper part of the wound, but this was only possible in one of my cases

Removal of the pouch is postponed for ten to fourteen days but can also be accomplished satisfactorily at a later date. During the interval the lymphatics in the tissue spaces of the neck will have had time to become sealed. After the first stage

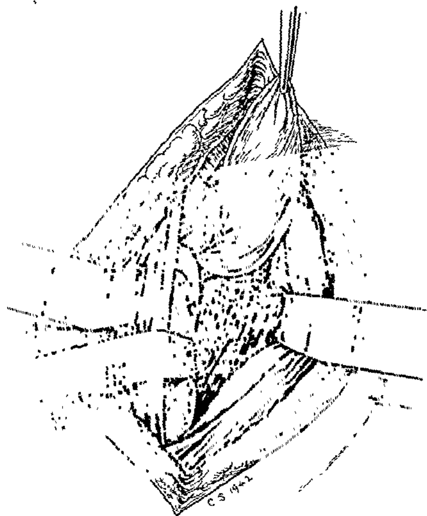


Fig 3—Shows displacement upwards of the pouch after it has been freed from its original position

the sac becomes considerably reduced in size through remaining empty, although the outer coat is thickened by œdema and cellular infiltration. If the sac is smaller than usual there may be some difficulty in finding it at the second operation, unless the level at which it was fixed has been noted.

There are two main methods of dealing with the sac. The

first consists in the free exposure and complete removal of the sac, the neck being dealt with as described in the one-stage operation. In the second method, first described by Wilkie and Hartley, a submucous resection of the mucosal lining is performed without opening up again the tissue planes of the neck. It is based on the fact that the mucosa is loosely attached and can readily be separated from the fascial coat. After the fundus has been exposed the top of the sac is removed, and the mucosal lining is stripped from the outer coats by blunt dissection to its junction with the pharynx. It is useful at this stage to pass a stomach tube from the mouth into the œsophagus in order to ensure that the separation has proceeded far enough and that none of the pharyngeal mucosa is removed. The mucosal tube is divided a short distance proximal to the level of its junction with the pharynx and closed by a purse-string catgut suture or by interrupted stitches, as appears indicated in the individual case. A strip of dental rubber is inserted within the fascial sheath down to the ligated stump, and the skin incision is partly closed around the drain.

Lahey, who has had more experience of the two-stage operation than any other surgeon, leaves a short cuff of mucosa, the edges of which are pushed inwards without closure by catgut ligature or suture which he believes has been responsible occasionally for a focus of residual infection.

I have used the submucous method of resection in four cases, and have found it simple and effective. The fascial planes of the neck were well shut off, and there seemed little risk of infection even if leakage were to occur. The mucosal tube was closed by ligation with a catgut purse-string suture, but in addition the surfaces of the adjacent fascial coat were sutured together over the stump. As the strip of dental rubber left in as a drain lay within the remains of the fascial sheath, there was little disturbance of the surrounding tissues In one case, in which the pouch was small, part of the fascial sheath was removed, and the remaining portion was overlapped and sutured over the mucosal stump to reinforce the weak area in the pharyngeal wall (Fig. 4).

After-Treatment—After diverticulopexy or a first-stage operation the patient is able to swallow fluids satisfactorily within a few hours, and can take a normal diet at the end of a few days After resection of the pouch some authorities prefer to feed the patient through a nasal tube which has been left in the œsophagus at the time of the operation. My own cases have been allowed

to swallow sterile water after the first twenty-four hours, and thereafter have been kept on fluids and soft foods for the first week. No leakage has occurred in any of the cases.

Results in Four Cases treated by Two-stage Resection.—All four patients were in relatively good condition at the time of operation. No complication developed in any of the cases after either the first or second stage, and all could swallow easily

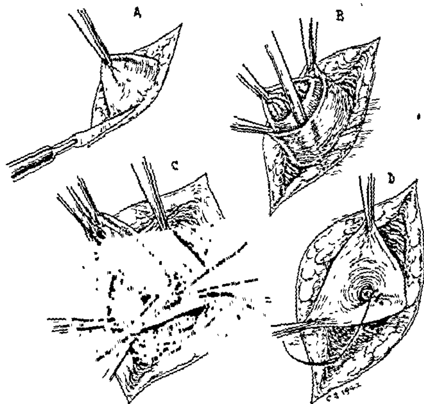


FIG 4—Resection of pouch—second stage A, Exposure of fundus. B, Top of sac removed Submucous dissection of mucosal lining commenced C, Ligation of mucosal tube close to its junction with the pharynx D, Suture of fascial sheath over mucosal stump

within a day or two of the first operation. No leakage occurred during healing of the wound after the pouch had been resected at the second stage.

The subsequent history of the cases, extending over periods ranging from a few months to eight years, has been entirely satisfactory There has been no recurrence of symptoms in any of the patients, and at the present time all are in good health and able to swallow normally

X-ray examination made after the first stage revealed without exception that the pouch was well elevated and that there was no

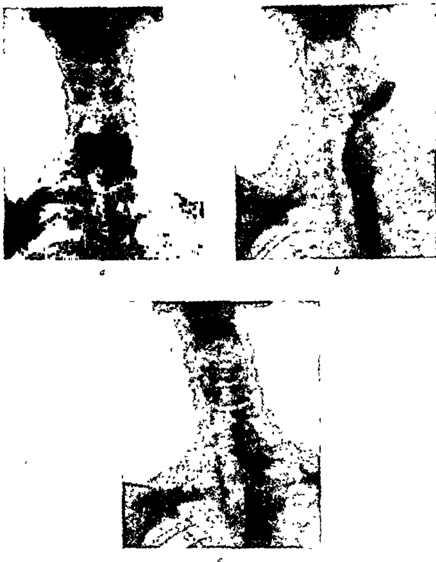


FIG 5 — (*a*) Pouch of moderate size before operation, (*b*) after first stage, (*c*) after resection

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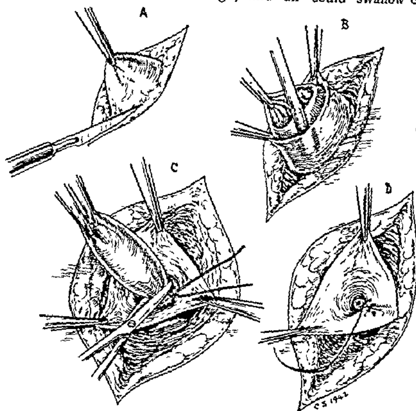


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especially large. In the latter cases the plates demonstrated a slight bulge at the former site of the pouch, although this was not associated with any delay or difficulty in swallowing.

Results in Four Cases treated by Diverticulopexy.—Three of the four patients were elderly, and two of them were in poor condition. The operation was performed in the remaining case because of the presence of a double pouch.

Case 1, *Mr S., aged* 72.—Symptoms for thirty years, culminating in complete dysphagia. General condition feeble, and auricular fibrillation present. Gastrostomy was performed, and fourteen days later the pouch was exposed and fixed in the inverted position. Within twenty-four hours the patient was able to swallow fluids freely, and the dysphagia, regurgitation and other symptoms were completely relieved. Convalescence was interrupted by an acute pleurisy which became purulent, requiring rib resection and drainage, but healing took place satisfactorily and the patient made a complete recovery.

The subsequent history of the case is instructive. The patient remained free from symptoms, but six years later reported with an inoperable epithelioma in the neck, which had commenced in the fundus of the pouch and which resisted treatment by irradiation. Dr Ewart Martin reported that the pharynx was not involved, and no difficulty in swallowing developed. Death resulted from secondary hæmorrhage.

The occurrence of malignant disease in this case illustrated one of the rare complications of pharyngeal pouch, which could have been avoided had the patient been fit enough to have the pouch resected at the time of the original operation (Fig. 6 (*a*, *b* and *c*))

Case 2, *Mr T., aged* 73.—The patient was in poor condition, suffering from a persistent pyrexia due to respiratory infection associated with the pouch. He made a slow but good recovery after operation, and the pyrexia did not return. The symptoms complained of were much improved, but complete relief could not be claimed, as occasionally traces of food were coughed up. The patient continued in active life till a year before his death from other causes at the age of eighty

Case 3, *Mr G., aged* 76—Typical symptoms for twenty years. Complete and permanent relief followed operation. Patient died at the age of eighty-four from an attack of purpura.

Case 4, *James M., aged* 67.—The case was most unusual in



a.



b.



c

FIG 6.—(*a*) Pouch before operation, (*b*) after diverticulopexy, (*c*) epithelioma arising from pouch six years later

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Summary and Conclusions

While the number of cases which I have had the opportunity of treating is comparatively small, the results obtained confirm those recorded in recent years, which provide ample evidence to prove that the mortality rate of the operation can be reduced to a very small figure. Is is right that this should be emphasised, as there is still a fairly general impression that the risks are such as to discourage resort to operation. This point of view has led to undue delay in some of the cases.

Lahey of Boston has reported 132 cases of pharyngeal diverticulum operated on, apart from a few treated by diverticulopexy, by the two-stage method, with but one death. Only three of the patients subsequently suffered a serious recurrence of symptoms. Some of his patients benefited from a post-operative dilatation of the sphincter. In my own cases an œsophagoscope or large stomach tube has always been passed at the operation, and so far there has been no need for further dilatation.

Harrington of the Mayo Clinic has recorded a personal series of 41 cases. In 25 of that number, mostly presenting large pouches, the resection was done in two stages, while in the remaining 16 cases, in which the sacs were small or of moderate size, the excision was completed in one stage. The results of the one-stage operation were very satisfactory, all the patients recovering, with primary healing, in 14 cases. These patients showed no recurrence of symptoms. Of the 25 cases treated by the two-stage method one died from infection. Twenty-one of this group obtained permanent relief.

It will be observed that the records of these exceptionally experienced surgeons show that only 2 out of a total of 173 cases operated on for pharyngeal diverticulum died as a result of the operation. If such results are to be obtained, it is important that cases should not be left too long, as the starved and debilitated elderly patient is invariably a poor risk for a major operation.

The late results of operation can also be described as highly satisfactory, and it is encouraging to find how seldom the symptoms recur when the age and condition of many of the patients are considered.

The observations of Harrington suggest that there should be considerable scope for the one-stage operation in the case of small sacs. Most surgeons, however, with less opportunity of dealing with these cases, will continue to employ the two-stage

that a large double pouch was present, and bilateral diverticulopexy was required. Symptoms had been complained of for one year. On some days he could swallow nothing, and on others, provided he was careful and took time, he could get a full meal down. For some months he had been aware of a swelling on both sides of the neck which could be emptied by pressure. X-ray examination showed a large pouch extending downwards to the suprasternal notch, with a bifid lower margin. On direct examination, Dr Simson Hall found that the two portions of the pouch were separated by a median raphé.

At operation the left lobe of the pouch was exposed, brought upwards almost to the skin surface after mobilisation, and fixed to the depressor muscles behind the thyroid ala. An œsophagoscope passed at this stage entered the right lobe of the pouch, which was still in its original position. A similar operation was therefore performed on the right side. The lower part of the pharynx appeared to share in the dilatation.

The patient made an excellent recovery, and from the first was able to swallow freely. He has had complete relief from all his former symptoms, and is now, eight years later, at the age of seventy-five, 2 stones heavier than before the operation and able for a full day's work.

Considering the size of the pouch, the short duration of symptoms was a remarkable feature of this case. It was satisfactory, although unexpected, to obtain such a complete relief of symptoms. A bilateral resection would have been a more dangerous proceeding, and could not have given a better result.

After the operation of diverticulopexy the pouch can still be demonstrated in X-ray plates after a barium meal. The lower margin, however, is always well elevated, and there is little tendency for the barium to collect (see Figs 5*b* and 6*b*).

The observations on these four cases justify the conclusion that the operation of diverticulopexy serves a useful purpose in certain cases The late occurrence of malignant disease in the pouch in one case and the incomplete relief of symptoms in the second case indicate that the operation should not be recommended in preference to excision when the condition of the patient and the nature of the pouch justify the more radical procedure.

THE SURGERY OF THE HYPOPHARYNX: POST-CRICOID CARCINOMA

By J. M. GRAHAM, M.B., Ch.M., F.R.C.S.Ed.
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CARCINOMA of the hypopharynx or post-cricoid area is a common form of malignant disease which entails much suffering on the part of the patient and seldom yields to treatment. In this respect it comes into line with carcinoma of the œsophagus which, with the exception of a few brilliant cases, has so far almost invariably proved fatal. Our knowledge of the subject is largely due to the original observations of the late Dr Logan Turner and to the contributions made by Mr Wilfred Trotter to the surgical technique.

In the treatment of post-cricoid cancer both surgery and radio-therapy have been tried in the past with indifferent results, but during recent years irradiation by X-rays or the radium mass unit has almost entirely supplanted operative measures. Surgery has never been employed to the same extent in carcinoma of the œsophagus, but the best method of treatment for malignant disease in this situation still remains a problem. The early favourable results recorded by Levitt led to a more intensive application of radio-therapy for œsophageal carcinoma, but, although some encouraging results have been obtained, there are few cases on record which can be regarded as cured, and surgeons have been showing in recent years renewed interest in the methods of surgical treatment. It is a matter of some importance to consider, in the light of the experience gained, whether surgery should not also be employed more frequently in the treatment of post-cricoid cancer.

My own observations are based on a series of 30 cases which were referred for opinion regarding the question of surgical treatment. All the patients had the advantage of expert investigation by a laryngologist.

Sex and Age Incidence

All except two of the thirty patients were women. This preponderance of the female sex is in agreement with all the

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procedure, which in any case is clearly indicated in the treatment of the larger pouches.

The following conclusions regarding pharyngeal diverticulum seem to be justified :—

1. The diagnosis can frequently be made from the history and clinical features alone.
2. It can be established in every case by a simple X-ray examination after a barium swallow.
3. Operation should be recommended unless the symptoms are comparatively slight.
4. The operation of diverticulopexy is of value if the patient is frail or in poor general condition.
5. The routine operation should be resection of the pouch in two stages. One-stage resection, if employed, should be limited to the treatment of small pouches.
6. The recorded series show that the mortality rate of the operation has been reduced to a very small figure. In the great majority of cases complete and permanent relief is obtained after operation.

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parts of the pharyngeal wall or the structure of the larynx. There is little doubt that the papillary type is of a lower grade of malignancy than the other forms.

On whichever aspect the growth commences, it tends to spread around the lumen, and sooner or later extends upwards towards the arytenoids Extension of the disease to the œsophagus is usually limited to the upper end. As the tumour advances it becomes adherent to the posterior aspect of the cricoid cartilage, and when the pyriform sinus is reached the structure of the larynx is soon involved Direct spread of the growth through the pharyngeal wall may affect the recurrent laryngeal nerves and the lobes of the thyroid gland. If the growth is extensive the larynx is projected forwards by a palpable mass Invasion of the thyroid gland is of clinical importance in that the enlargement of the thyroid may be regarded as the primary condition and treated as such

Secondary spread to the lymph glands on one or both sides of the neck is usually a relatively late phenomenon. When the primary disease is already advanced, an enlarged gland in relation to the internal jugular vein opposite the angle of the jaw is frequently present, but once the lymphatic system is invaded it is not uncommon to find glands involved in remote parts of the neck or mediastinum. In one of my cases a solitary gland appeared on the right side of the neck six months before the first complaint of dysphagia The gland was regarded as tuberculous, and was removed in the Out-Patient Department. When the pathologist reported the presence of a squamous epithelioma the case was thought to be an example of a branchial carcinoma, and it was only later that symptoms appeared which drew attention to the primary disease in the hypopharynx. When the lymph glands are obviously involved it will usually be found that the local disease is already too advanced for radical excision

Clinical Features

In the early stages the patient complains of slight difficulty in swallowing, which at first may be intermittent, or of some discomfort or abnormal sensation on deglutition Occasionally the obstruction to swallowing has come on suddenly without previous warning, and has persisted after a piece of meat or solid food has lodged in the throat.

In many of the cases seen in hospital the disease is already

published statistics. In a series of 98 cases of post-cricoid carcinoma recorded by Logan Turner, 85 of the patients, or 86 per cent., were women. As Trotter has pointed out, carcinoma of the laryngo-pharynx is one of the most remarkable examples in pathology of the primary site of the tumour being determined by the sex of the patient. Carcinoma of the epilaryngeal portion of the pharynx, involving the epiglottis, aryepiglottic fold, pyriform sinus and lateral wall, while not wholly confined to men, shows a strong preference for the male sex.

There is a difference also in the age incidence in the two sexes. Carcinoma of the post-cricoid area is common in women at a relatively early age, which may be estimated, according to Trotter, as at least ten years less than the average age at which the epilaryngeal portion of the pharynx is affected in men. Logan Turner found that the average age of 85 women with post-cricoid carcinoma was forty-five, while the average age of the 13 men in his series was fifty-seven. More than half of the women in my own series of 30 cases were below the age of fifty when the disease appeared.

Cancer of the epilaryngeal region and of the hypopharynx are characterised, not only by differences of age and sex, but also by a variation in the clinical features. It is highly important, when an operation is to be undertaken, that the exact site of the growth should be known, as the surgical procedure must be planned according to the part involved.

Pathology of Post-cricoid Cancer

Operation on a considerable number of cases has given an opportunity of studying the pathology.

Malignant disease in the hypopharynx is invariably an epithelioma, and four main types can be recognised. There is a polypoid type with large, projecting masses, frequently pedunculated, and not involving as much of the pharyngeal wall as the appearances suggest An infiltrating type with superficial ulceration is relatively common ; it tends to constrict rather than to project into the lumen A third form appears as a malignant ulcer with indurated edges and excavated base As regards metastases and spread these types show little variation in the degree of malignancy. The fourth variety has a coarse papillary structure which projects on the surface and may extend more widely than the other types before infiltration involves the deeper

parts of the pharyngeal wall or the structure of the larynx There is little doubt that the papillary type is of a lower grade of malignancy than the other forms.

On whichever aspect the growth commences, it tends to spread around the lumen, and sooner or later extends upwards towards the arytenoids. Extension of the disease to the œsophagus is usually limited to the upper end. As the tumour advances it becomes adherent to the posterior aspect of the cricoid cartilage, and when the pyriform sinus is reached the structure of the larynx is soon involved. Direct spread of the growth through the pharyngeal wall may affect the recurrent laryngeal nerves and the lobes of the thyroid gland. If the growth is extensive the larynx is projected forwards by a palpable mass. Invasion of the thyroid gland is of clinical importance in that the enlargement of the thyroid may be regarded as the primary condition and treated as such.

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Clinical Features

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In many of the cases seen in hospital the disease is already

advanced, with marked dysphagia and pain on swallowing or referred to the ear. Such patients frequently have a repeated accumulation of mucus in the throat, with a tendency to coughing or hoarseness, and there may be an enlarged gland in the neck or a palpable swelling behind the larynx to indicate the probable diagnosis. There are exceptional cases in which the dysphagia is still slight or even absent, and the appearance of an enlarged gland has been the first indication of the disease.

The diagnosis can rarely be made at an early stage of the disease without a direct examination. It can seldom be determined by the laryngoscope alone, except in the later stages. It is important, therefore, in all early and doubtful cases that the patient should be referred to a laryngologist for investigation without delay. In many cases coming to hospital the diagnosis at once suggests itself, and the disease is found to be already advanced and inoperable.

X-ray examination after a barium swallow may show the barium retained in the pharynx, and the irregular outline of the shadow sometimes suggests the nature of the condition The patient, however, may be unable to retain the barium when the difficulty in swallowing is considerable, and the X-ray examination is often of less diagnostic value than might be expected It will, nevertheless, differentiate the condition from one of pharyngeal pouch and, as a rule, from cases of the Plummer-Vinson syndrome, in which, unless the degree of spasm is very marked, there is only a momentary hold-up before the barium passes into the œsophagus. It should be noted that an X-ray photograph in the lateral position without barium is likely to give positive information in cases of post-cricoid carcinoma, as the larynx is seen to be displaced forwards and separated by the shadow of the growth from the cervical vertebræ (McWhirter) (Fig. 1).

In many cases the laryngologist reports that the disease has already involved the larynx and other structures, and is too extensive for radical operation. Even in apparently favourable cases, however, the extent of the disease cannot always be definitely ascertained until the parts have been exposed at operation. It is sometimes necessary, therefore, after free exposure has been obtained, to abandon the idea of a radical operation, which can be safely done if the pharynx has not been opened.

It can readily be understood that the extension of the disease,



Fig. 1.—Displacement of larynx forwards by post cricoid carcinoma

with increasing dysphagia, hoarseness and respiratory embarrassment, is responsible for a degree of suffering in the later stages which can scarcely be exaggerated.

Duration of Symptoms

Except in four of my cases the symptoms had been complained of for periods varying from a few weeks to nine months, with an average of four and a half months. The four exceptional cases gave a history of slight trouble with deglutition for many years. The long period during which difficulty in swallowing had been experienced by these patients made it extremely improbable that a carcinoma could have existed throughout the whole of the time covered by the history The patients explained that they had to take their food slowly, and had not troubled about their condition until swallowing became really difficult or painful. The previous history was not always given spontaneously, and it may be that in some of the other cases a sufficiently detailed history had not been taken to elicit minor degrees of dysphagia in preceding years.

Logan Turner stated that in his series of 98 cases approximately one-third of the patients gave a history of long-standing minor degrees of dysphagia. At the same time he made the important observation that a long antecedent history of dysphagia was only obtained from the female patients. This association between a simple spasmodic form of dysphagia and carcinoma of, the hypopharynx in women has been noted by numerous observers. Paterson and Brown Kelly were the first to describe the changes present in the pharyngeal mucosa in what has since become known as the Plummer-Vinson syndrome. The atrophy and decreased elasticity of the pharyngeal mucosa, with its tendency to crack and bleed on instrumentation, have been attributed to defective nutrition associated with the dietetic and iron deficiency so commonly observed in women of the working class, particularly during the child-bearing period. There seems little doubt that, for some obscure reason, these changes are pre-cancerous in certain individuals. Paterson and others have recorded observations over a considerable period on cases of this simple type of dysphagia which later developed malignant disease of the hypopharynx. It is interesting to note also that Ahlblom of Stockholm, in a special investigation, obtained a history of long-standing mild dysphagia in a high percentage of his cases of post-cricoid cancer, but only, as a rule, after careful questioning.

It is obviously of great importance that careful enquiry should be made in all cases of hypopharyngeal carcinoma with regard to the history or signs suggestive of a pre-existing Plummer-Vinson syndrome. In the great majority of patients of the Plummer-Vinson type the anæmia, glossitis and other symptoms can be completely relieved by the administration of an adequate amount of iron and a well-balanced diet. If it can be definitely established that the association is a common one, then the prevention of hypopharyngeal carcinoma in a considerable proportion of individuals becomes a possibility.

Treatment

An attempt may be made to eradicate the disease by operation or by irradiation. The radical operation requires the removal of a considerable segment of the pharynx including the upper end of the œsophagus. As it is never possible to suture the divided ends together, it is necessary in planning the operation to provide a skin flap for subsequent reconstruction of the gullet. If the disease has already involved the larynx, the operation will entail simultaneous laryngectomy, a procedure of great magnitude which is seldom likely to be successful and is rarely justified. Not infrequently the patient's life may be made more endurable by a palliative operation such as gastrostomy or tracheotomy.

A permanently successful result has been obtained only in exceptional cases after radical operation, and it is not surprising that treatment by irradiation has largely supplanted surgery in recent years. My last radical operation in the Royal Infirmary for post-cricoid carcinoma was performed more than seven years ago

Results of Treatment by Irradiation.—Six cases in this series were treated by irradiation. Four of the patients received a course of X-ray therapy. Dramatic improvement followed the treatment in one case , but, although the disease seemed temporarily to have disappeared, it soon recurred, and the patient died ten months later. Two further cases died within five months, while in the remaining case the reaction was severe and death occurred before the treatment was completed.

In two cases radium needles were implanted after the growth had been freely exposed by dissection One patient survived for four weeks and one for five months. Both patients suffered from hoarseness and other signs of local reaction, and the dysphagia was not relieved.

These records are disappointing, but the observations are too limited to be of much value, and I am indebted, therefore, to Dr McWhirter, Radiologist to the Royal Infirmary, for fuller information on the subject.

Dr McWhirter has recently reviewed a series of 292 cases of carcinoma of the upper air passages treated by irradiation during the ten-year period 1930-39. The hypopharynx was the most commonly affected region, the term being employed in the restricted sense used by Trotter to denote the post-cricoid area and the adjacent lateral and posterior walls of the pharynx. In 57, or 19·5 per cent., of the cases the location of the disease was hypopharyngeal. X-ray therapy or the radium mass unit was the method of treatment carried out except in a few cases.

The three-year survival rate for each anatomical site has been analysed for the years 1930-37, the results showing a marked variation in the prognosis according to the site of the disease. In the case of intrinsic carcinoma of the larynx, for instance, a survival rate of 67 per cent. was obtained. During the period 46 cases of cancer of the hypopharynx were treated, and the result is seen in the following table, which gives the three-year survival rate for each part of the laryngo-pharynx :—

	Hypopharynx	Lateral and posterior wall.	Epiglottis	Arytenoid and aryepiglottic fold	Pyriform fossa
Alive	0	2	3	2	2
Total . .	46	21	12	17	22
Survival rate	0	10 per cent	25 per cent	12 per cent	9 per cent.
Net survival rate = 8 per cent					

The analysis shows that only 8 per cent of the cases of carcinoma of the various parts of the laryngo-pharynx survived for a period of three years after treatment It will be noted that *not a single patient out of 46 treated for carcinoma of the hypopharynx* was alive at the end of three years.

Dr McWhirter adds the following note :—

" Carcinoma of the hypopharynx has presented an extremely difficult problem In spite of the fact that the patients have acute distress at an early stage of the disease, the condition is often overlooked. Direct examination, as opposed to indirect, is

necessary for the diagnosis when the disease is at an early stage. The main symptom is difficulty in swallowing, and because no abnormality may be noted on indirect examination, the dysphagia is often considered to be of nervous origin. On questioning the patients it is obvious that the possibility of malignant disease is frequently overlooked when the patient first seeks medical advice. The only rule, therefore, to adopt when a patient complains of pain or hoarseness or difficulty in swallowing is to refer him immediately for complete investigation. The great majority of the cases treated were extremely advanced, and many of the patients had even the greatest difficulty in swallowing water. Their general condition was poor, and any form of treatment was unlikely to be successful. The majority of the cases did not receive even temporary improvement. In some more recent cases better immediate results have been obtained, but the period is too short to permit of any conclusions being drawn It may be that surgery would be a better method of treatment if the case is at a sufficiently early stage to permit of complete removal of the diseased area."

Results of Surgical Treatment.—In the series of 98 cases reviewed by Dr Logan Turner in 1920 it is reported that only 10 cases were submitted to radical operation. Five of these patients died at intervals of from five to eighteen months, and three were alive and well without trace of disease six, seven and fourteen months after operation. Two patients were alive two and a half and ten years after operation, and the former of these cases, on whom I had the privilege of operating, is still alive and well more than twenty-four years later.

The expectation of life after the diagnosis had been made in the inoperable cases varied from a few weeks to seven months, with an average of four months

A radical excision of the post-cricoid area was performed in 12 of my own series of 30 cases, and in addition there were 3 cases in which the operation was combined with laryngectomy. In the earlier cases a simple excision of the hypopharynx was performed, and no attempt was made to reconstruct the gullet. The operation was completed by implanting the open end of the œsophagus in the lower part of the neck, and the patient was subsequently fed through a tube Four of the five patients on whom this operation was performed lived for six, twelve, fourteen and eighteen months respectively, and, except in the case of one

who developed an intercurrent infection, all showed evidence o recurrence at the time of death.

The following is the history of the remaining case, still aliv twenty-four years after operation :—

Mrs M., aged 29.—Difficulty in swallowing for two years Latterly unable to take solids, and fluids only with difficulty anc severe local pain. No palpable mass or enlarged glands in the neck., Larynx normal. The case was examined by Dr Logar Turner, who found a circular mass of disease occupying the post-cricoid space, infiltrating the mucosa and covering the



FIG. 2—Œsophagus implanted in neck after resection of post cricoid carcinoma Patient alive twenty-four years after operation

posterior surface of the cricoid cartilage and the posterior pharyngeal wall The pathologist reported the growth to be an epithelioma.

Operation, 10.9 17—Exposure was obtained by an incision along the anterior border of the sternomastoid muscle on the left side. The sternomastoid and carotid sheath were retracted, and the left lobe of the thyroid was displaced medially after division of the superior and inferior thyroid arteries No enlarged glands were found. After the upper end of the œsophagus had been freed, the inferior constrictor muscle was divided and the lower end of the pharynx separated from the cricoid. A complete segment about 2½ inches in extent and including the upper end of the œsophagus was excised As apposition of the divided ends of the gullet was impossible, the opening in the pharynx was closed and the upper end of the œsophagus was sutured to the

lower angle of the skin incision. The wound healed in a few weeks.

Since the operation the patient has been fed through a funnel attached to a short piece of stomach tubing. She takes an

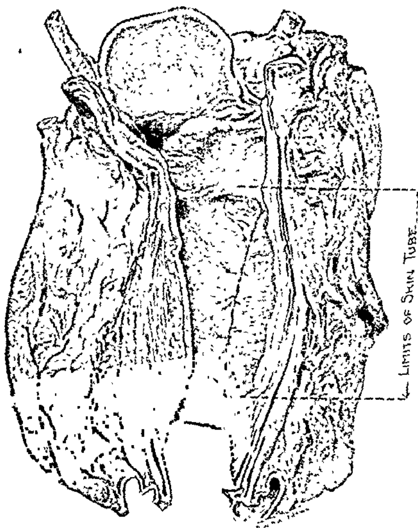


Fig 3.—Pharynx reconstructed by skin flap, six months after operation. Patient died suddenly. No evidence of recurrence.

ordinary diet, enjoying various flavours, and, after chewing her food, she collects it in a cup and transfers it to the filler. In spite of her inability to swallow, the patient's nutrition has been perfectly maintained throughout the long period which has elapsed since the operation (Fig. 2).

Reconstruction of the Pharynx by Skin Flap (Trotter's Operation).—In 7 cases the operation of lateral trans-thyroid pharyngotomy was performed, with provision of a skin flap for reconstruction of the pharynx. Two of the patients died four days after the operation, and two survived only for a few months. The operation was successfully completed in 3 cases, all of whom were able to swallow normally. One of the cases died suddenly six months later without evidence of recurrence (Fig. 3) The second patient died at the end of eighteen months with widespread glandular metastases, although up till two months before her death her general condition had been satisfactory (Fig. 4 (*a* and *b*) and Fig. 5 (*a*, *b*, *c* and *d*)). The third case made an excellent recovery, and has been able to swallow normally since the operation was completed over fifteen years ago.

Mrs J., aged 47.—Complained of something sticking in the throat and of pain over a period of four months. Dr J. S. Fraser reported on direct examination a warty type of growth in the post-cricoid area extending upwards, mainly on the posterior wall. A biopsy was performed and the pathologist reported the growth to be an epithelioma.

Operation, 15.10.26.—Ether anæsthesia induced and continued through a low tracheotomy opening. A rectangular skin flap was outlined with its base over the sternomastoid muscle on the left side, the flap extending for 2 inches to the right of the midline. The upper margin of the flap was at the level of the hyoid bone, the lower incision being made across the neck immediately above the tracheotomy opening. Exposure of the growth entailed removal of the left lobe of the thyroid gland. No enlarged glands were found After the depressor muscles and the inferior constrictor had been freed, the posterior two-thirds of the ala of the thyroid cartilage were removed The lower part of the pharynx and the upper end of the œsophagus were then freely exposed. The anterior border of the sternomastoid muscle was sutured over the carotid sheath to the pre-vertebral muscles A complete segment of the hypopharynx, including the upper end of the œsophagus and a portion of the posterior pharyngeal wall was removed The skin flap was tucked inwards in front of the pre-vertebral muscles and sutured above to the posterior edge of the opening in the pharynx and to the right free edge of the pharyngeal mucosa and below to the divided end of the œsophagus, which was then fixed by sutures to the margins of the surrounding

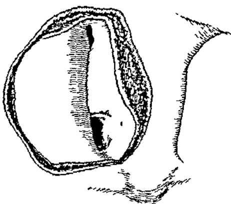


a.

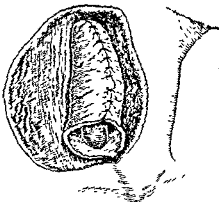


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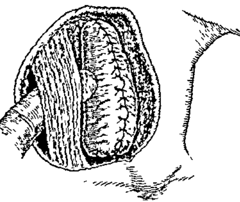
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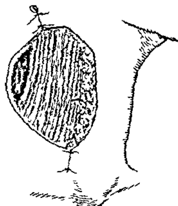
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FIG. 5.—Shows various steps in the reconstruction of the gullet by tube of skin.

skin. By undermining the skin on the right side of the neck the gap left by the transposition of the flap was almost entirely covered over. A stomach tube was introduced into the œsophagus for a few inches for feeding purposes. After this stage of the operation a deep skin gutter was left in the side of neck, communicating with the pharynx above and the œsophagus below.

Reconstruction of the Gullet, 31.1 27—An incision was made around the margin of the opening in the pharynx, and continued downwards on the medial side around the œsophageal opening and upwards on the lateral side about 1 inch from the edge of the gutter. After the skin had been elevated on both sides the



FIG 6—Appearance after reconstruction of pharynx by skin flap Patient well and swallowing normally fifteen years after operation

edges were united by closely placed catgut sutures, care being taken that no pockets were left at either end where the skin tube joined the mucosa of the pharynx and œsophagus. By undercutting it was possible to bring the edges of the surrounding skin together, and to cover almost completely the reconstructed gullet. The patient was fed through a nasal tube for five days, and thereafter was able to swallow fluids freely No leakage occurred, but signs of a stenosis soon appeared at the junction of the skin tube and the œsophagus. It was necessary to make a small incision into the skin tube, through which a finger was passed into and through the narrowed area. At the same time slight angling at the junction was corrected A few days later a large-sized stomach tube was easily passed through the mouth well down into the œsophagus, and the patient continued to pass the tube herself occasionally for a few months. There was no further

trouble with swallowing, and she has remained in excellent health. She takes a normal diet, including solids of all kinds, and swallows as well as she did before her carcinoma appeared over fifteen years ago (Fig. 6).

Excision of the Post-cricoid Area combined with Laryngectomy.—There were three patients who had a combined laryngectomy and excision of the post-cricoid area. In all three cases the disease was extensive. Two of the patients died fourteen days after operation, and the remaining case showed signs of recurrence at the time of her death eight months later. The operation is a severe and mutilating one, and is seldom indicated.

Palliative Operations.—Gastrostomy was performed in nine inoperable cases, and tracheotomy was required in addition in three of the patients with stridor and respiratory embarrassment. The advisability of performing a gastrostomy has been questioned. Anyone, however, who has witnessed the painful end of these patients suffering from increasing thirst, aggravated by the constant loss of saliva which they are unable to swallow, can have little doubt of the value of such a minor operation in relieving their distress, although the prospect of prolonging life is little increased.

Summary and Conclusions

From the observations recorded in this series it is apparent that little improvement in the results can be expected, whatever method of treatment is adopted, unless the cases can be diagnosed at an earlier stage If a patient is seen when the symptoms are slight and indefinite, she should be referred without delay to a laryngologist for a full examination A growth of the post-cricoid area may be seen with a laryngoscope when the disease is advanced, but it is only by a direct examination that the early stages of the condition can be recognised and confirmed by biopsy.

The connection between the Plummer-Vinson syndrome and cancer of the hypopharynx deserves to be stressed. It has been noted by many experienced observers, and was present in four of my cases It seems more than a coincidence that both the Plummer-Vinson syndrome and cancer of the hypopharynx should be confined, with rare exceptions, to the female sex in early middle life. The epithelial lining of the hypopharynx shows a special tendency to cancer, and the spasm of the sphincter and the slight changes in the mucosa in patients with the Plummer-Vinson syndrome seem sufficient in some individuals to initiate the

malignant change. Except in the few cases which require dilatation the symptoms and signs of the Plummer-Vinson syndrome can be completely relieved by full doses of iron and an adequate diet. It seems, therefore, that there is a reasonable prospect of preventing the development of cancer in certain individuals suffering from this type of anæmia with dysphagia, provided that the treatment is timely and thorough.

The results obtained by radio-therapy, from which so much was hoped, have so far been disappointing. Not one of the 46 cases of post-cricoid cancer treated in the Royal Infirmary during the period 1930-37 has survived for as long as three years.

The results of operation have also been far from good. A radical operation was performed in 15 cases, in three of which the larynx in addition was removed. Two of the 15 patients have survived in good health for periods of fifteen and twenty-four years respectively. The evidence in favour of surgical measures cannot, therefore, be regarded as convincing, but it provides some justification for the conclusion that in the meantime, till further advances are made in X-ray or radium therapy, radical operation should again be considered as the method of treatment when the disease is not too far advanced.

In conclusion, I wish to express my indebtedness to Dr McWhirter for the information he has kindly supplied regarding the treatment of malignant disease of the upper air passages by irradiation.

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PROGRESSIVE MIDDLE EAR DEAFNESS

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AT the present time when the nation is straining every effort to dispose its man power to the best advantage, both in the armed forces and in industry, any preventable circumstance or condition which appreciably diminishes the flow of recruits to the forces, or limits the usefulness of any member of the community, assumes a new importance. It is the duty of every one who is in any way responsible for maintaining the health of the working population to take note of this, and to examine our methods with a view to decreasing the loss of otherwise healthy men and women and to determine whether our results can be improved.

That this loss is a reality is obvious to those who have the duty of examining and grading recruits who suffer from ear disease.

The intention here is to take stock of the position, to describe the methods of dealing with the problem of deafness, and to indicate the lines along which work is being carried on to improve results still further.

The beginnings of deafness of the middle ear type are to be found in the earliest years of life. The majority of young adults trace their trouble back to childhood, so, as in many other problems in medicine, early recognition and treatment is one of the most important methods of dealing with the disability. At present, however, disease must be treated as it is encountered.

Progressive middle ear deafness falls into three categories:

(1) Deafness due to obstruction and catarrhal conditions usually outside the middle ear cleft;
(2) Suppurative conditions of the middle ear;
(3) Non-suppurative diseases of the middle ear which are progressive

Catarrhal Conditions

Into the first group fall such conditions as enlargement and infections of the tonsils and adenoids, sinusitis, nasal obstruction,

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and Eustachian catarrh which frequently comes from these diseases.

Although found in the adult, these troubles operate chiefly in children to cause progressive deafness and are frequently discovered by means of routine school inspection and by the testing of hearing by mass methods. The cure is comparatively simple and consists of removal of the tonsils and adenoids and drainage of the infected sinus This is followed, if necessary, by inflation of the Eustachian tubes, and usually is all that is necessary to restore hearing to normal level. It is the neglect of this simple treatment which so often lays the foundation of chronic ear disease in adult life.

These facts are so well known that there is little need to elaborate them, and the second group comprising the suppurative diseases will be considered more fully.

Middle Ear Suppuration

Although the majority of the patients treated are adults, the fact is that treatment should commence at a much earlier age than it is usually possible to accomplish. Whenever an attempt is made to bring this about serious difficulty is encountered.

It might be thought that with the developed school service early recognition and treatment of suppurative otitis media would be almost automatic, but there is reason to believe that the highest incidence of otitis media occurs between the years of one and five—that is, in the pre-school period when there is not the same opportunity for systematic inspection.

Diagnosis of Deafness.—Even in schools recognition of deafness is not always simple. Numbers of children who suffer from middle ear disease are unaware of the fact, and working mothers are frequently too harassed, or too uninterested in the children, to find it out for themselves, and so it is left to the school medical officer to discover the presence or absence of disease. It would be unfair to expect the school medical officer to diagnose all cases of middle ear disease, and the examination required to discover this would entail an impracticable expenditure of time.

The problem is being more effectively dealt with in another way. Since the introduction of the audiometer the scientific testing of large numbers of school children is simplified. A gramophone is used, the volume of which can be varied in accurately calibrated steps. The children are made to write down

what they hear from the gramophone through ear-phones, and in this way the deaf children can be quickly discovered, and the number of individual examinations required is reduced to manageable proportions. Finally, children requiring special examinations are filtered into the hands of the school otologist, who is called upon to decide treatment for the cases in which it is required.

In this system of diagnosis there are many possibilities of error and fallacy, but it is still in process of development and, it is hoped, will give increasingly accurate results.

Incidence of Middle Ear Disease.—By various methods of examination it has been calculated that 5·3 per thousand children requiring treatment or observation suffer from middle ear suppuration.

In special surveys of school children the incidence of otitis media has been found to be as high as 48·2 per thousand.

This is the background of the patients who are treated in the nose, throat and ear department for chronic middle ear suppuration, and it is hoped, when the results of these careful methods of investigation and early institution of treatment bear fruit in a few years' time, that the number of adults complaining of deafness will materially decrease.

As it is impossible to cover all the types of suppurative otitis media which are encountered, and which, indeed, are not important for the present discussion, only these types which are responsible for a steady deterioration in hearing are mentioned here.

Types of Suppuration.—Periodic ear discharge is frequently seen, which becomes worse with a cold in the head, and is characterised by a large amount of mucoid discharge in the ear. Such a condition is, as a rule, due to infection of the Eustachian tube, which again is caused by infection in the nasopharynx or the nose

Operations on these cases give, as a rule, very poor results so far as a dry ear is concerned, but happily they do not usually cause marked deterioration of hearing.

The type of case which causes the greatest loss is that in which there is deep-seated disease of bone. This is marked in those in whom polypus formation and granulation formation are found in the posterior and superior parts of the middle ear, in the attic, in the antrum, and occasionally in the mastoid cells. Sometimes with no overt sign there is extensive disease owing

to the formation of cholesteatoma, which is a tumour-like mass caused by desquamation of epithelium within a closed area. This process causes pressure necrosis of the surrounding structures and may even penetrate into the brain. The infection of such a mass gives rise to some of the most serious complications which are associated with ear disease.

Treatment.—Diagnosis of the extent of the disease in these forms of suppuration can frequently be made by inference only, so the majority of cases have, first of all, a prolonged course of conservative treatment. This treatment may consist of simple cleansing of the ear, or the ear may be subjected to special forms of treatment directed towards sterilising the middle ear cavity, such as zinc ionisation. It is only after the failure of this treatment, and only when observation over a number of months shows that the hearing is steadily becoming less, that operation is undertaken.

There are three objects in the treatment of chronic middle ear disease :—

(1) The provision of safety for the patient.
(2) The preservation of hearing
(3) The production of a perfectly dry ear, which requires no treatment

Considerable work has been directed during the past years towards the removal of dangers to the patient, and at the same time the preservation of hearing.

There are three methods of treatment commonly employed in mastoid surgery. There is, first of all, the simple or conservative mastoid operation usually known as the "Schwartze" operation, which consists of drainage of the mastoid air cells and which aims at leaving the middle ear in as normal a condition as can be achieved. There is no structural or functional change in the middle ear cavity This is used chiefly for the cure of acute suppuration.

The next best known type of operation is the radical mastoid operation. This lies at the other end of the scale from the first operation, in that it is a complete exenteration of the whole middle ear cavity, which is rendered necessary by the fact that disease has completely destroyed the middle ear mechanism.

Midway between these operations we have the modified radical mastoid operation The modified radical mastoid operation aims at removing chronic disease and freeing the patient

what they hear from the gramophone through ear-phones, and in this way the deaf children can be quickly discovered, and the number of individual examinations required is reduced to manageable proportions. Finally, children requiring special examinations are filtered into the hands of the school otologist, who is called upon to decide treatment for the cases in which it is required.

In this system of diagnosis there are many possibilities of error and fallacy, but it is still in process of development and, it is hoped, will give increasingly accurate results.

Incidence of Middle Ear Disease.—By various methods of examination it has been calculated that 5·3 per thousand children requiring treatment or observation suffer from middle ear suppuration.

In special surveys of school children the incidence of otitis media has been found to be as high as 48·2 per thousand.

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their work for a day, and other arrangements required for a complete survey, in war time, made it necessary to eliminate a large number of patients who could not be reached and who, therefore, cannot be included from the point of view of judging results. The present survey is therefore limited, and has been confined to those patients about whom very full notes are available, and who, in most cases, lived within easy reach of the hospital, a point of very great importance for the patient. These restrictions emphasise certain important facts in treatment and the importance of some economic problems which become apparent.

Results of Operation.—Out of the cases of radical mastoidectomies 59 have had to be excluded upon this basis, and from the modified radical mastoidectomies 63 have had to be excluded. After this sifting of cases it is possible to arrive at a figure which represents the number of cases completely healed and dry—in other words, those which may be judged successful, and it is found that 226 cases in all are successful, and 25 cases are judged failures.

In the case of the radical mastoidectomies the percentage of success is 80, and in the modified radical mastoidectomies the percentage is 95.

No case has been included in this series which has not been observed over a prolonged period, and no case is assumed to be a healed, dry ear until it has been observed as such for a period of months.

TABLE I

Chronic Middle Ear Suppuration

Total number of operations—500
Modified radical mastoidectomy—261.
Radical mastoidectomy—239
Total number of personal cases—373

	Radical mastoidectomy	Modified radical mastoidectomy
Number of operations	162	211
Successful	85	141
Unsuccessful	18	7
Discarded	59	63
Percentage successful	80 per cent.	95 per cent.
Deaths	Nil	Nil

After-treatment—The conduct of after-treatment has been shown to be the most important part of the treatment, and continuous care by the same surgeon is essential in order to obtain

from all danger, but at the same time preserving the middle ear mechanism so that the patient's hearing will be undamaged by the operation, and in all probability improved to a great extent.

At present the prevailing view is that where chronic middle ear disease exists the radical mastoid is the operation required, except for certain specialised types of suppuration, and as a consequence a higher proportion of radical mastoid operations is done as compared with modified radical mastoid operations.

The late Dr J. S. Fraser, who was one of the leading authorities on this subject, reported a series of cases in 1930, which shows clearly the position between these two methods of treatment at that time. In his series of 499 mastoid operations 98 were modified radical mastoidectomies and 401 were radical mastoidectomies.

This view is reflected in the relatively greater emphasis which is placed upon the radical operation in most textbooks.

Conversations with specialists in other centres show, however, that preference is swinging from the radical mastoid operation to the modified radical mastoid, and the necessity for the preservation of hearing function is obtaining proper recognition. Although in the majority of cases we find that after the radical mastoid operation hearing function is on the average rather improved than diminished, the improvement is only a small percentage of that which can be gained by the use of the more conservative procedure. The functional results obtained by the radical mastoid operation are not sufficient for the rehabilitation of the patient according to present-day standards. Earlier diagnosis and earlier operation would permit the preservation of hearing in many cases where at present it is lost For this reason a special study has been made during the last ten years of the modified radical mastoid operation

In the department under the writer's charge close on 600 mastoid operations have been carried out for the cure of chronic ear suppuration during this period. Personal responsibility is assumed for more than 400 cases, and the following brief analysis is based upon this series. Of these, 211 were modified radical mastoidectomies, and 162 were radical mastoidectomies The remainder were more elaborate surgical procedures for the cure of intracranial complications.

In attempting to analyse such a series as this it will be readily understood that the difficulty of locating young people, the difficulty of travel, the necessity of taking patients away from

Of all the methods of cavity treatment, the skin graft by this method has given much the best results. A very few have had to be repeated owing either to insufficient operation in the first instance, or to the operation having been done under conditions which were really too advanced for the modified procedure.

TABLE II

Treatment of Operation Cavity
Dry and Healed

	Per cent.
Skin graft (secondary)	96
Syringing and scarlet red drops	82
Boric and iodine powder insufflation	45
Periosteal graft	20
Iodoform worsted and argyrol pack	20

Average healing time for three-fourths of each group was nine weeks in each instance.

With the exception of a very small number of such cases, all the cases treated by secondary skin grafting have become completely healed and the cavities completely epithelialised. No other form of after-treatment has given anything approaching such satisfactory results These results, however, are only obtained in patients who are able to continue to attend for treatment; the nine weeks, and sometimes more, which are required for healing are frequently too long for the average working man or woman to give up to medical treatment when they are otherwise fit for work. Recently, experiments have been made with amniotic membrane as a cavity lining The number of such cases treated by this means is too small to be of any value statistically, but the early results which have been obtained raise the hope that this again will be an improvement on the skin graft method, as it can be used with less technical difficulty, and the after-treatment is considerably simplified

Progressive Non-suppurative Middle Ear Deafness

The third type of deafness to be considered is non-suppurative middle ear deafness. Within this group is included a number of conditions Chief amongst them is otosclerosis Diagnosis between these types of disease in many cases cannot be made with absolute accuracy without microscopic examination of bone, but otosclerosis is probably the commonest and is the most important to the present discussion.

good results. The patient must be warned that this attention may be necessary for many weeks after the actual hospital stay has been completed. It is for this reason that such a large number of cases have had to be discarded when judging what can be done with this operation. The majority are those who have been sent home under the care of their own doctor or under the care of district nurses because economic circumstances rendered it impossible for them to remain longer in hospital.

This fact raises questions of considerable importance. If such a high percentage of completely healed and dry ears is obtained in the patients who live near the hospital, it seems unfortunate that those who are not in the same favourable geographical position have to run the risk of failure of the operation in at least one respect.

The treatment and after-care by which the results recorded were achieved cannot be handed over to practitioner or nurse, but require the attention of one specially trained in the work. The constant endeavour, therefore, has been to evolve some method of cavity treatment whereby patients can be discharged from hospital after a period of about three weeks with the certainty that in a high percentage of cases the patient's ear will be completely healed and dry in the average healing period.

Many forms of treatment have been used, such as simple mopping of the cavity, syringing, and the instillation of scarlet red and other antiseptic drops; packing with various substances, the insufflation of powders, have all been tried. More elaborate methods have been used, such as grafting with periosteum, grafting with skin both as Thiersch grafts and pinch grafts, and covering the cavity with a substance such as amnioplastin.

The skin graft treatment of mastoid cavities was tried fully by the late Dr John S. Fraser. He used the method of inserting a Thiersch graft into the cavity at the end of the operation. This method was not found to give satisfactory results, because being planted upon bare bone there was no possibility of the skin having adequate nourishment, and in the vast majority of cases it sloughed out in large pieces.

The method which is carried out now is that the wound is allowed to granulate, and when there is a good carpet of healthy granulation tissue covering the bone the skin graft is inserted, with the almost invariable result that it takes well and adheres to the granulation tissue. The period required before this can be done may vary from one to two weeks according to the patient.

Albert Gray thought that mechanical stresses, combined with the failure of the vasomotor reflex responsible for dealing with the most of these stresses, was the underlying condition. Others, such as Otto Mayer and Witmaack, favoured the developmental origin of the abnormal bone. The possibility of an endocrine function being partially responsible was scoffed at by the majority of these observers. The fact that it is more frequent in women, usually commencing at, or just after, puberty, and becomes manifestly worse during pregnancy, directed attention at a very early stage to the idea that internal secretions might be responsible Few of the workers on the pathology of the condition would admit a *connection of any kind* *Recent developments in endocrinology*, however, have rendered it likely that help may be expected from this direction.

The interest of the workers mentioned was pathological only. When the question of treatment was raised, apart from the general principles of removing septic foci, teeth, tonsils, etc., no help could be given to the patient. The patient was told to use lip-reading, or a hearing aid, and apart from this no encouragement was given that the patient could do other than sit down and wait the onset of complete deafness. That this defeatist attitude should be accepted is impossible, and experimental work has been done with the object of bringing some relief to these sufferers

Treatment.—*Recent research has taken two lines, endocrine* and operative. An attempt has been made to use recent knowledge and discoveries in the use of hormones and vitamins to supply the deficiency responsible for the breakdown of the vasomotor reflex, if we accept Albert Gray's theory for a moment. This work is still only at its beginning; it is a long-term investigation, for one or two or more years will be required before it will be possible to state whether or not the selected cases are benefiting All that can be said in the meantime is that a series of cases is under investigation, and the results which have been obtained are encouraging A debt is gratefully acknowledged to Dr Macpherson of the Endocrine Clinic for his assistance in the examination and investigation of these patients with a view to ascertaining what deficiency there may be, and the balancing of this deficiency with suitable therapeutic measures

It is evident that the restoration of hearing by operative means in a disease which is progressive, and which, according to some authorities, may eventually affect the whole eighth nerve tract, is

I. Simson Hall

Otosclerosis

Patients may give a history of increasing deafness without any history of middle ear suppuration—that is, pain or discharge. Frequently there is a history that the deafness runs in the family, and examination usually shows that the cochlear reactions indicate *middle ear deafness only, the cochlear nerve being intact and* normal.

There are, in addition, a number of other symptoms, such as tinnitus and occasional giddiness, which are variable. Atypical cases are found, but there is no room to discuss them here.

Happily this condition is not of very great frequency; it varies from 5 to 10 per cent. of all ear conditions. Unfortunately, the sufferers from this form of deafness are chiefly young, healthy adults of both sexes, although more frequently females than males. They are usually around their twenties, at a period when *their higher education is being completed, and the prospects* of life are opening up in front of them. At this point they discover that their chosen profession is impossible for them, and they may be faced with the inability to pursue the lucrative form of employment, in training for which they have wasted years and money.

The *professions, in most cases, are closed to them.* Sometimes the patients are young men in their thirties who have been conscious of slight deafness for a great many years. Frequently they have wives and young families, and they suddenly realise that it is impossible for them to carry on with their employment. It is then too late for them to take up some other line of work, and domestic tragedy may stare them in the face.

A great deal has been written regarding the etiology and pathology of this form of deafness, in particular, of otosclerosis. The late Dr J. S. Fraser made this subject his own, and he was one of the pioneers in the investigation of its pathology. The *outstanding fact* is that *changes take place in the bone,* usually around the promontory and the footplate of the stapes in the middle ear, whereby the movement of the stapes is seriously limited and the transmission of vibrations across the middle ear to the cochlea is hindered It may proceed to complete immobilisation of the stapes with a very severe degree of deafness for the patient.

Etiology.—There are several theories with regard to its etiology. The late Dr Fraser believed that slight inflammatory changes in the middle ear played a leading part in its causation.

Albert Gray thought that mechanical stresses, combined with the failure of the vasomotor reflex responsible for dealing with the most of these stresses, was the underlying condition. Others, such as Otto Mayer and Witmaack, favoured the developmental origin of the abnormal bone. The possibility of an endocrine function being partially responsible was scoffed at by the majority of these observers. The fact that it is more frequent in women, usually commencing at, or just after, puberty, and becomes manifestly worse during pregnancy, directed attention at a very early stage to the idea that internal secretions might be responsible. Few of the workers on the pathology of the condition would admit a connection of any kind. Recent developments in endocrinology, however, have rendered it likely that help may be expected from this direction.

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dealing only with the necessity of the moment, and that treatment which does not include within its scope the fundamental deficiency remains incomplete. For this reason the two lines of enquiry are complementary.

Operative Treatment.—For the restoration of hearing operative treatment is required The principle underlying this operative treatment is that the fixation of the stapes renders it increasingly difficult for the vibrations of sound to take place within the cochlea and to influence the organ of Corti. When the stapes becomes completely immobilised, the round window being the only remaining opening, vibration is impossible as the fluid is incompressible and there is no other opening which will enable the vibration to take place.

What the operation, therefore, sets out to do is to provide another opening which will again permit mobility of the fluid within the labyrinth. That this does in fact take place is the experience of every one who has carried out this operation, and it was first reported by Jenkins in 1913, in London. Successive surgeons have experimented with this treatment, but it is only within the last five years that sufficient success has attended the treatment to encourage those investigating its possibilities to persevere. The leaders of recent progress are Professor Holmgren of Stockholm, and M. Sourdille of Nantes.

That the hearing can be dramatically improved by making an opening in the labyrinth is an established fact. The chief difficulty is to keep the opening in the labyrinth patent and so preserve the improvement which has been won. Closure of the opening by new bone formation, or fibrous tissue formation, takes place in the months immediately succeeding the operation, so that increasing deafness is again experienced by the patient. It is chiefly along the lines of technical improvement that experiment has been carried out in order to prevent bone regeneration.

The opening is made, as a rule, in the horizontal canal, or that part of it close to or adjoining the vestibule. The opening is made in various shapes and sizes in the bony covering and the endosteum, leaving the membranous labyrinth containing the endolymph intact.

The surgical technique required to carry out this procedure is of a very advanced nature *The opening has to be cut in a canal* measuring under 2 mm. wide without damage to the contained tube which lies a fraction of a millimetre from the surface. An operating microscope is necessary, with special instruments which



PHOTOMICROGRAPH 1 —Middle ear after completion of first part of operation. Showing incus with malleus behind it, head of stapes, tendon of stapedius muscle, roof of vestibule and plastic flap laid back on left



PHOTOMICROGRAPH 2 —Incision of incudomallear capsule, preliminary to removal of head of malleus



PHOTOMICROGRAPH 3 —After removal of head of malleus Cut neck of malleus can be seen on left



PHOTOMICROGRAPH 4 —Dissection of horizontal canal almost completed

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PHOTOMICROGRAPH 5 —Opening in horizontal canal Opening can be seen to extend over roof of vestibule anteriorly Canal appears to be empty Transparent membranous canal does not show



PHOTOMICROGRAPH 6 —Taken immediately after No 5 Horse hair rests on membranous canal which shows within the bony canal (The canal was not prepared in any way and the photograph is untouched)



PHOTOMICROGRAPH 7 —Plastic flap replaced Outline of incus can be seen covered with membrana flaccida



FIG 8 —Ordinary photograph of cavity showing drum membrane and flap in place

will permit the surgeon to work accurately to within fractions of a millimetre.

After the canal has been opened the fistula formed in the canal is covered by means of a plastic flap. The flap consists of skin covering the roof of the external auditory meatus, together with the upper part of the tympanic membrane. This is mobilised in such a way that it covers the opening made in the canal. Plastic flaps such as these have within them the factors which so often nullify the operation, as they stimulate the growth of bone (Figs. 1-8).

Many substances and methods have been used to prevent the formation of bone, such as radium, gold leaf, and diathermy.

An original contribution to the solution of this problem has been the use of amnioplastin. This has for some time been used to prevent the adhesions of brain tissues to operation scars when repair of cranial injury has been undertaken. On this analogy it seems possible that fibrous tissue formation between the membranous canal and the flap used for covering the fistula may be prevented.

Amnioplastin has been used in the later cases carried out, but these are too recent to provide information, as a period of several months must elapse before it is possible to judge whether the operation has been a success

It has been stated that these operations are unjustifiable, presumably because they incur too great a risk with too small a prospect of success. So far as risk is concerned, in no case in the whole of this series of 31 cases has there been any infection of the labyrinth as a result of the operation. The same experience is reported by other operators elsewhere, and in fact the care with which this operation is normally approached and the precautions which are taken have rendered the pathological material available practically nil.

Results.—As time has progressed results have improved. To judge this series of operations on total results over all operations done would be misleading, because the operations were undertaken at first with no magnification, with incomplete equipment, and with a very scanty knowledge of the technical difficulties. These had to be learnt by experience and experiment as there were no standards Later methods and later instruments are so immeasurably superior that recent results only are representative of what improvements are possible.

Progressive Middle Ear Deafness

The increase in hearing is variable and general factors influence the gain or loss. The most favourable case is that of a young person—say, eighteen to thirty years—not too seriously handicapped by deafness and with no trace of nerve deafness.

The audiometer chart shows such a case with the gain in hearing obtained.

There is another aspect of the matter which must be mentioned, but which cannot be demonstrated by graph or chart. This is the psychological effect upon the patients of a successful operation of this kind. The outlook upon life is changed completely. Instead of continuously increasing depression, hope comes again into their lives and is reflected immediately in their appearance, their manner, and even in the clothes they wear.

This is necessarily an incomplete statement, for the work itself is still hardly out of the experimental stage; but it is well worth the patience and trouble entailed, for, measured in terms of human happiness, there is no more important problem in otology

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The results so far obtained can be seen in the accompanying table. Experience has shown that if the new opening into the labyrinth is kept open then the gain in hearing remains, so that

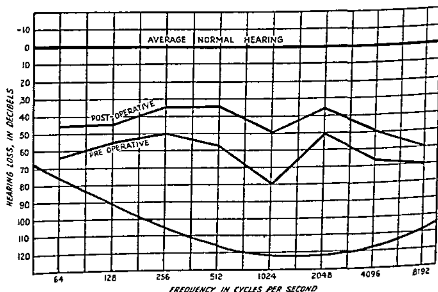
TABLE III

Fenestration of Labyrinth

Total number of cases—31

Effect on hearing, over all operations—	
Unchanged	10
Worse	1
Improved	10
Operations with improved methods (2 years)	17
(Two cases are under six months and are not included.)	
One-stage operations	13
Two-stage operations	2
Hearing improved	10
Hearing unchanged	5
Fistula patent	13
Fistula doubtful	2

success is measured to some extent by the number of times the fistula remains patent. It is found also that if the fistula remains for five to six months it is likely to be permanent.



AUDIOGRAM — Chart showing typical post-operative gain in hearing

stage restoration of the circulation and of normal function can be expected to follow relief of the cord from pressure. Continued ischæmia leads to permanent destruction within the cord, and we know that in some cases this destructive process may be long delayed, then proceed disastrously perhaps within a matter of hours. When the compressing agent is a localised slowly-growing tumour, for instance, a meningioma or a neurinoma of a spinal nerve-root, the cord possesses a remarkable power of moulding itself into the diminishing space available within the theca, so that on cross-section it may come to lie like a crescent around the tumour indenting it. But even so, a time comes when the circulation can no longer be adequately maintained and the progress of symptoms thereafter is rapid.

It is common clinical experience that after lumbar puncture the signs indicative of compression of the cord may be accentuated; perhaps a definite upper level of sensory loss may become apparent for the first time. The explanation is again to be found in local impairment of circulation within the cord; the fluid pressure in the lumbar sac is reduced, perhaps to zero, by the puncture and the normal fluid pressure above the level of the lesion impacts the cord more firmly down into its restricted bed. It is always good practice, therefore, to re-examine every case after lumbar puncture

I need not dwell upon the obvious importance of careful clinical investigation in the diagnosis of lesions of the spinal cord and nerve-roots. As is usual in neurological cases the history must be detailed, accurate and preferably set forth chronologically. The examination of the patient should be conducted in surroundings warm and comfortable enough to overcome any tendency to shivering and physiological muscular hypertonus due to exposure. Accurate sensory examination requires sustained attention by the patient, and this may not be attainable if he is distracted by personal discomfort.

Lumbar Manometry

This is certainly the most important of the accessory methods of investigation The demonstration of a partial or complete spinal subarachnoid fluid block often provides the final and conclusive evidence that a space-occupying lesion is present. In performing the test, the jugular compression should be applied on both sides simultaneously. Unilateral jugular compression is of value only when the patency of one lateral sinus is in doubt.

SURGICAL LESIONS OF THE SPINAL CORD AND NERVE-ROOTS

By G. L. ALEXANDER, F.R.C.S. (Edin. and Eng.)
Associate Assistant Neurological Surgeon, Royal Infirmary

THIS subject is a wide one, and I have no intention of trying to deal systematically with the numerous conditions affecting the spinal cord and nerve-roots which may come within the ambit of the surgeon. I propose to discuss some general principles and indicate the lines along which our methods of handling these cases have been modified in recent years by increasing experience.

The spinal cord is a delicate structure, carrying within small compass tissues mediating motor, sensory and trophic functions for the body, and consequently a lesion of limited extent, but implicating the cord, makes its effects widely apparent. The pathological states involved are varied; they include traumatic lesions, acute and chronic inflammatory processes, tumour formations and congenital anomalies. The vertebral column or any one of the structures contained within the vertebral canal may be primarily affected. In the cases calling for surgical treatment the operative technique is in most instances directed towards relieving pressure upon the spinal cord or nerve-roots.

The results obtainable after timely surgical intervention are frequently among the most gratifying in the whole field of neuro-surgery. It should be noted that *timely* intervention is specified, and I should like to emphasise the potential urgency of every case showing a syndrome suggestive of compression of the spinal cord. Too often in the past surgical treatment has been delayed until the bladder failed to empty, catheterisation with its aseptic paraphernalia became necessary and at last the case was referred to hospital or to the surgeon. Such an easy-going attitude is no more excusable than delay in dealing with a gangrenous appendix.

The important part played by circulatory disturbance within the cord in the development of the symptoms and signs is not commonly realised. Pressure upon the cord first affects the veins, causing local congestion, suboxæmia, and probably œdema, resulting in dysfunction of the affected nervous tissue. At this

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stage restoration of the circulation and of normal function can be expected to follow relief of the cord from pressure. Continued ischæmia leads to permanent destruction within the cord, and we know that in some cases this destructive process may be long delayed, then proceed disastrously perhaps within a matter of hours. When the compressing agent is a localised slowly-growing tumour, for instance, a meningioma or a neurinoma of a spinal nerve-root, the cord possesses a remarkable power of moulding itself into the diminishing space available within the theca, so that on cross-section it may come to lie like a crescent around the tumour indenting it. But even so, a time comes when the circulation can no longer be adequately maintained and the progress of symptoms thereafter is rapid.

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The promptness and rapidity of fall of fluid in the manometer tube on release of the jugular veins is of more positive value than the rate and extent of the preceding rise of fluid level. Incomplete compression of the jugular veins might cause a rather slow rise of the fluid level, but there can be no dubiety about the sudden cessation of the pressure upon the veins. Finally, the patient should be relaxed and breathing quietly during the test.

In quite a number of cases simultaneous cistern and lumbar manometry is helpful. This provides a valuable check on a doubtful lumbar manometric observation and also permits comparison of the constituents of the fluid above and below the suspected lesion.

Laboratory examination of the fluid obtained by spinal puncture is important. The total protein content is frequently raised in the conditions under present consideration. Throughout the country it has been common experience that the protein readings from different laboratories are apt to vary consistently, and this is in part at least due to the method used. The most accurate of all is, of course, the micro-Kjeldahl analysis, but this is too time-consuming for routine use. We have recently been favourably impressed by the constancy and accuracy of the results given by the Lovibond colorimeter

Radiographic Examination

This is of obvious importance when the vertebral column is injured, but radiological assistance should be sought in all cases. Important information may be missed in "single" films, and whenever possible stereoscopic films should be requested. Fine details of bony structure may be altered; enlargement of an intervertebral foramen may give the clue to the presence of a neurinoma extending out along a nerve-root, the pedicles may be compressed and the distance between pairs of pedicles may be increased when a very slowly-expanding lesion lies within the vertebral canal. On occasion it is even possible to see scattered flecks of calcification in a spinal meningioma. These are only some examples of the assistance afforded by good X-ray films.

The injection of heavy radio-opaque oil into the theca by cistern or by lumbar puncture is frequently requisite when clinical and radiological examination fail to provide an accurate localisation of the lesion, or when, as is often the case, we wish

to have all the information obtainable in planning our surgical attack with precision. The French "Lipiodol" was much used, but had the disadvantage of gradually liberating free iodine and whenever that had occurred the oil acquired irritant properties. Even when recently-prepared oil of light colour was used, we found it responsible occasionally for a persistent lumbo-sacral radiculitis. We have not been alone in this experience, and the present tendency is to abandon use of the oil except in small amounts of 1-2 c.c. Recently iodised oils for which greater stability is claimed have become available; time will show whether they may be used with impunity. Dr J. C. White of Boston on his recent visit to Edinburgh recommended a method he had found successful in reclaiming a large part of the oil from the theca. The patient lies prone on the X-ray table. A lumbar puncture needle, preferably of rather wide bore, is inserted at the usual interspace until its point lies near the anterior wall of the theca. With the help of the screen the oil can be aspirated mixed with cerebrospinal fluid. We have repeatedly been able to reclaim 75 per cent. and more of the injected oil in this manner.

Although the oil is usually injected by cistern puncture with the patient sitting, it may be injected into the lumbar sac for the study of a high cervical obstructive lesion. The patient is then tilted increasingly head-downwards on the X-ray table and the oil is followed on the screen as it gravitates toward the upper part of the vertebral column.

I turn now from the general to the particular, selecting for comment some only of the many conditions which might come within the scope of this lecture.

Traumatic Lesions of the Spinal Cord

If, as the result of injury to the vertebræ, the vertebral canal becomes narrowed so as to cause pressure upon the spinal cord, steps should be taken without delay to relieve that pressure. Exceptions may be made when the lumbar fluid contains a considerable quantity of blood, indicating irreparable damage to the neural structures contained within the theca, or when there has been *immediate* total abrogation of motor and sensory function below the level of injury. In very many cases, however, evidence of a total transverse lesion of the cord is apparent only on recovery from a period of unconsciousness occasioned by a concomitant head-injury; in other cases the circumstances of the

accident may have prevented attempts by the patient to move the limbs for some little time after the injury. A compression fracture of the body of one vertebra without damage to the related articular processes may be reduced by hyperextension combined with traction in the long axis of the trunk. This procedure should, however, be reserved for those cases of compression fracture showing, at most, slight neurological dysfunction.

With the above exceptions, then, we have adopted the policy of being guided by the findings on lumbar manometry. If there is a partial or complete spinal subarachnoid fluid block, and the lumbar fluid is clear or contains little blood, we decide to operate. The operation of choice may be laminectomy or open reduction of a dislocation; in cervical injuries the application of skeletal traction will frequently suffice.

We are aware that in many cases this policy runs contrary to classical teaching, but bearing in mind the harmful effect of continuing pressure upon the circulation of the spinal cord it seems logical to intervene at the earliest possible moment. Valuable time is being lost if we are to wait, perhaps for several days, to observe evidence of returning conduction of impulses through the damaged segments; thus, indeed, we may throw away the chance of obtaining any functional recovery. It is true that in very many cases irreparable damage is done to the cord at the instant of injury, and if we are prepared to operate on the indications provided by lumbar manometry, many disappointments must be expected Yet in the knowledge that the procedures involved carry no appreciable operative risk, we feel that every effort should be made to spare the patient from a paraplegic existence.

Pressure on the cauda equina should always be relieved.

The treatment of fractures and dislocations involving the cervical vertebræ has been greatly facilitated by the introduction of skeletal traction applied to the skull. This method has many advantages over the irksome chin-halter. It is comfortable, yet permits much heavier traction weights to be employed, movements of the lower jaw are unimpeded, and more positive control is obtained over the direction of the correcting force. The risk of pressure sores in the occipital region is avoided, and this is important if surgical exposure of the cervical vertebræ should later be indicated. The traction may be maintained for weeks without risk of cranial osteitis, and a plaster-cast can be applied without difficulty before the apparatus is removed.

Fig 2 —Radiographic appearance before treatment, showing the uncommon posterior atlanto-axial displacement

Fig 3 —Improvement attained in six days with skull-traction (11 lbs)

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The following case is illustrative:—

A young officer received a bullet-wound of the left cheek during the raid on Vaagso Island. The main force of the bullet was expended in destroying the lower alveolus on the left side. The bullet came to rest in the soft tissues of the naso-pharynx and was later lifted out therefrom. The patient immediately experienced the effects of concussion of the spinal cord, but recovered from this in a few minutes. Injury to cervical vertebræ was suspected, and although the radiological evidence was

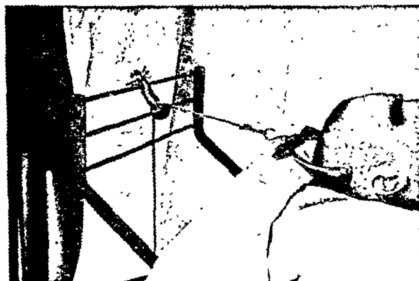


FIG 1.—The skull-traction apparatus in position.

negative a plaster-cast was applied. In due course he was referred to a base hospital for further treatment of the facial and pharyngeal injuries. Spinal cord functions were normal and the plaster-cast was removed About two and a half months later, while sitting up in bed washing, he suddenly felt the tips of the thumb and fingers of both hands going numb, and this sensation persisted although objectively no sensory loss was demonstrable. Soon afterwards he found that voluntary full flexion of the head occasioned a tingling sensation distally in both upper limbs and often in the calves simultaneously. The paræsthesia disappeared when flexion ceased. He had no disturbance of bladder function.

Radiological examination now showed a gross displacement of skull and atlas backward upon the axis. The odontoid process

union occurs between the odontoid process and the body of the axis, provided the parts are immobilised by bone-grafting. The subsequent stability of the vertebral column appears to be permanent. Fusion of the upper four cervical vertebræ alone still permits some useful movement at the lower vertebræ.

Spinal Tumours

This comprehensive and rather inexact term embraces a variety of neoplasms differing in their morbid anatomy and histological characteristics. If one excludes secondary malignant disease, in the majority of cases seen the tumour is benign and can usually be extirpated completely. Delay in treatment of these cases is therefore all the more to be deprecated

Even in the less favourable types of primary tumour to be found in the spinal cord (angioblastoma), in the epidural space (locally infiltrating tumours of unclassifiable cell-type), or in the vertebræ (several varieties of myeloma), X-ray therapy is able to accomplish what is beyond the surgeon in the way of radical cure. In such cases, however, surgery plays its part in providing immediate relief of pressure, and the opportunity of biopsy enables a histological diagnosis to be made so that X-ray therapy may be planned appropriately.

The syndrome of spinal tumour is typically one of *progressive* sensory and/or motor dysfunction referable to the spinal cord or nerve-roots. Quite frequently localised root-pains are among the earliest symptoms and an accurate localisation may thereby be made, especially if corroborative clinical signs are to be elicited on examination. Early loss of pain and thermal sensation will suggest an intramedullary lesion, but with increasing experience neuro-surgeons are becoming less confident in their pre-operative opinion as to the morbid anatomy in cases of spinal tumour Disturbance of blood supply in the affected and related segments of the cord may be responsible for bizarre effects, notably in the upper cervical segments which are dependent largely on the spinal branches of the vertebral arteries The pressure of a tumour makes its effects felt throughout the whole thickness of the cord, and it is usually unprofitable to hazard a guess at the position of the tumour relative to the cord from an analysis of the symptoms and signs. In a few cases an incomplete Brown-Sequard syndrome will suggest an intrinsic lesion of the cord but benign extramedullary tumours are also responsible for this

had been fractured at its base and was carried backwards along with the anterior arch of the atlas. Close study of the X-ray films taken on admission to the base hospital showed a faint tell-tale line of rarefaction through the base of the odontoid process; there was no doubt that the base of the odontoid had been fractured by the impact of the bullet and that gradual luxation had occurred after removal of the supporting plaster-cast. The Blackburn skull-traction apparatus was applied to the skull under local anæsthesia and alignment of the atlas and axis was much improved

Here I should like to make passing reference to the valuable device described by Cone and Turner, which we have found of considerable assistance in the treatment and nursing of these cases. As usual, the rope attached to the traction appliance passes round a pulley to reach weights suspended a short distance from the ward floor. The pulley is so made that it can travel freely from side to side, running by a second pulley-wheel on a horizontal bar set out a convenient distance clear of the bed. With this arrangement the direction of pull is not materially altered when the patient is turned on one side, since the rope, pulley-block and weights travel freely along to the required new position.

Returning again to the case of the officer, reduction was far from complete and there was no doubt that luxation would soon recur on removal of the traction. Accordingly (ten days ago) the dorsal aspect of the upper four cervical vertebræ was exposed by operation, with skeletal traction still maintained. The atlanto-axial articular facets could not be brought into good apposition owing to intervention of soft tissues carrying the important vertebral arteries, but with the aid of a powerful instrument made specially for the purpose, controlled pressure was brought to bear on the posterior tubercle of the atlas and improved alignment was secured. Two lengths of rib-graft were procured from the thorax. The grafts were lashed in place with wire loops passing through holes in the occipital bone near the foramen magnum and also passing under each lamina. The accessible articular facets down to C 4-5 were scarified to promote fusion.

The case for bone-grafting in some injuries of cervical vertebræ has been well made out by Cone and Turner. Fusion operations are indicated in atlanto-axial dislocations and in fracture-dislocations at any cervical level when the deformity is readily corrected and will as readily recur. From their experience Cone and Turner state that, contrary to current belief, osseous

preceding the radiation of pain down one or other lower limb is a common feature but is not constant. A history of backstrain or other trauma is quite often not obtainable, and in this connection the type of patient and his occupation should be borne in mind; for instance, the miner working at the coal-face must daily be exposed to many twists and strains, any one of which would deeply impress, say, a sedentary worker, and would readily be recalled to mind.

On examination in a typical case there is evidence of an organic lesion of the lumbo-sacral nerve-roots—depression of cutaneous sensation, or perhaps hyperæsthesia, in one or more root-fields; perhaps wasting and fibrillation of muscles in the affected limb; and depression or loss of a tendon reflex, very commonly the ankle-jerk. In most cases the normal lumbar curve becomes flattened and even lumbar kyphosis may be found A lumbo-sacral tilt away from, or rather less frequently towards, the affected side is often present in addition. These abnormal postures of the spinal column are due to reflex muscle-spasm and usually they disappear when the patient is seated, with hips and knees flexed, thus relaxing tension on the sciatic nerve The upper part of the sciatic nerve trunk may be tender on pressure, and sometimes the inflammatory reaction in the nerve may extend down as far as the major branches, so that even the common peroneal nerve may be palpably thickened and tender. We know that this inflammatory reaction also spreads up the roots intrathecally, and it is evident that we have often to deal with a quite extensive radiculo-neuritis although the exciting lesion is so localised.

The diagnostic problem is one of selecting out those cases in which the symptoms are being maintained by the mechanical pressure of a protruded disc

Pennybacker, at Oxford, has recently differentiated anatomically a diffuse yielding of the annulus fibrosus from localised protrusion of the nucleus pulposus through the annulus and posterior longitudinal ligament The clinical syndromes can not yet be differentiated, and he is of opinion that the post-operative results in cases where the annulus bulges diffusely into the vertebral canal are apt to be unsatisfactory. Our experience of such cases is recent and limited, but, so far, we have no reason to be displeased with the convalescence and early results We have removed as much as possible of the offending annulus and have removed also the pulpy nucleus

syndrome. In short, then, in the majority of cases neurological study alone should indicate the level of the tumour, but may be misleading as to details of pathology at the affected level.

Protrusion of the Intervertebral Disc

Although herniation of the nucleus pulposus backwards through the annulus fibrosus and posterior longitudinal ligament into the vertebral canal had been recognised by pathologists and described as far back as 1896 by Kocher, it was not until 1911 that the first clinical account was given by Goldthwait. His case was one of supposed sacroiliac strain, subjected to manipulation under anæsthesia. On recovery from the anæsthetic the patient exhibited paraplegia and sensory loss corresponding to a lesion of the cauda equina, and without delay Dr Cushing was asked to perform laminectomy. At operation a large mass of tissue was found in the epidural space anterior to the theca in the lower lumbar region compressing the cauda equina. By a process of exclusion Goldthwait arrived confidently at the correct conclusion as to the pathology involved.

The literature subsequent to this publication contains occasional reports of individual cases in which the spinal cord was compressed by so-called chondromata of intervertebral discs at cervical, thoracic and upper lumbar levels. We should now recognise these cases as examples of disc protrusion occurring at levels in relation to the spinal cord Such cases are still relatively rare, in our series there is so far only one example, a bilateral protrusion at C 6-7, with a cord-compression syndrome possessing no distinctive features.

It was only when protrusion of the nucleus pulposus came to be recognised as an ætiological factor among the sciaticas that the true frequency of pathological states of the lower lumbar discs was discovered. Love and Walsh published from the Mayo Clinic a few years ago an analysis of 100 consecutive cases of disc protrusion at all levels, which showed that in 76 per cent. of the series protrusion occurred at the fourth-fifth lumbar or lumbo-sacral interspaces.

For practical purposes then, the cases present with the clinical picture of a lumbo-sacral radiculitis, complaining of recurrent attacks of unilateral pain, and possibly paræsthesiæ, in the lower lumbar and first sacral root-fields The symptoms are exaggerated on coughing and straining. Lumbar backache, frequently

it is an easy matter to nibble away the lower border of the lamina, when adequate access to the ligament can be obtained. Through the window thus made into the vertebral canal the nerve-root in its epidural course and the theca may be retracted medially, exposing the disc. The laminæ, spinous processes and interspinous ligaments are not disturbed. One would not hesitate to explore on both sides with this fenestration technique.

The functional results obtained with early active movement and graded exercise during convalescence have contributed in influencing us to advocate operation rather than conservative treatment for these cases.

Before leaving this subject, brief reference must be made to the rather infrequent cases of massive protrusion of the nucleus pulposus in the lumbar region. This is the type of case already referred to in connection with Goldthwait's early publication. The syndrome is that of compression of the cauda equina as a whole, and usually manipulation of the spine under anæsthesia has been employed in the previous management of the case. Such cases must be relieved by operation without delay. Owing to the fact that the sensory roots are involved central to their ganglia, sensory recovery in the sacral root-fields may be incomplete or absent unless very prompt action be taken. There is therefore some danger attendant on spinal manipulation in cases where the symptoms are due to pathology of the intervertebral disc.

Congenital Anomalies

Spina Bifida.—All must be familiar with this relatively common developmental abnormality in its many forms. If surgical treatment is to be undertaken, I should like to emphasise the urgency of the matter in cases where the epithelium covering any part of the sac is very thin or deficient. The sac should be cleaned with strict aseptic precautions immediately after birth, so that a reasonably aseptic field may be preserved Operation, if decided upon, should be carried out within a few hours of birth

We select for operation only those cases showing no extensive paralysis distally in the lower limbs The reflex motor reactions to pin-prick on the dorsum and sole of the foot are particularly observed. A patulous anus, absence of the anal reflex or constant dribbling of urine are contra-indications to operation. We should also decline to operate on cases already showing signs of hydrocephalus

Laboratory examination of the lumbar spinal fluid is of assistance. A total protein reading approximating the normal value of 30 mgm./100 c.c. is in favour of a disc protrusion A reading over 60 mgm./100 c.c, especially if accompanied by any rise whatever in the cell-count, will make us suspect a primary toxi-inflammatory radiculitis, or, alternatively, an epiduritis—fibrosis and venous congestion around the nerve-roots in the epidural space. The latter conditions respond well to epidural injection of weak novocain solution in bulk, but, as would be expected, are often not improved by surgical exploration.

Radiological examination is not of much positive assistance apart from excluding tumour of the sacrum or vertebræ involving the roots. Normally, the lumbar interspaces vary greatly in width. "Wedging" of an interspace, as seen in antero-posterior view, is occasionally seen and may be accepted as strongly suggestive of a pathological disc.

During the stage when all clinics were using heavy lipiodol as an aid to diagnosis, contrast radiography played an important part in the investigation of each case, but for reasons already detailed it is preferable to avoid the use of iodised oil We prefer now to act on clinical judgment alone.

I come now to the treatment of these cases. We are seeing them with increasing frequency, especially now that such a large proportion of the young adult male population is engaged in strenuous Service training. We are becoming less and less impressed with the efficacy of conservative treatment and have no hesitation now in recommending exploration.

In the first two cases of our series the operation was a formal laminectomy and exposure of the lumbo-sacral nerve-roots. The nodule of protruded disc was approached transdurally. Those early cases demonstrated the characteristic swelling and injection of the root or roots, extending up as far as could be seen in the operation field, certainly several centimetres above the point at which the root pierced the theca.

Hemilaminectomy then became for a time the operation of choice, and latterly the approach to the disc was entirely extradural.

The final improvement in technique has been excision of ligamenta flava only, as suggested by Love, leaving the axial skeleton intact. The distance between adjacent laminæ varies in different patients and at different levels in the one patient. When the ligamentum flavum is at all overhung by the lamina above,

cord and nerve-roots. In cases amenable to surgical treatment it should be the aim of all concerned to ensure that surgical exploration precedes and thus forestalls the onset of bladder symptoms. Retention of urine is the usual problem encountered, but in a few cases (injury or tumour involving the conus medullaris) the bladder and sphincters are atonic, resulting in dribbling incontinence and an empty bladder. When, through retention of urine, the bladder is allowed to become overdistended the contractility of the bladder musculature is rapidly impaired and simultaneously the risk of urinary infection becomes very great.

Three lines of treatment are open to us in dealing with the retention of urine. If the patient's neurological disability is expected to be very transient, catheterisation with strict aseptic and antiseptic precautions at intervals not exceeding eight hours may be adopted In some cases catheterisation may be avoided by injection of one of the choline drugs, provided that emptying of the bladder is thereby complete

For the case requiring sustained attention to the bladder by far and away the best method is tidal drainage. This requires an in-dwelling catheter which must be changed every three or four days, so that the point of the catheter may not rest continually against one point on the bladder mucosa and cause ulceration. The in-dwelling catheter alone, even with twice-daily irrigation, is a bad method and should not be employed Tidal drainage apparatus can be assembled from standard hospital equipment of rubber and glass. We used the pattern advocated by Munro of Boston, but have lately found the arrangement described by Bellis (1940) works more consistently. The principle is simple. A drip-apparatus containing a weak solution of any urinary antiseptic is set up by the bedside and is connected indirectly to the catheter. The bladder gradually fills with fluid from the drip-apparatus and simultaneously, of course, with urine from the ureters. When the intravesical pressure reaches a head of water not exceeding three inches above the level of the pubis, a syphon is established and the bladder is rapidly emptied As soon as the syphon effect is established, air is drawn into the system through a narrow by-pass insufficient to break the syphon until the flow of urine and fluid from the bladder is arrested, at which point the syphon is broken and the whole cycle repeats itself, approximately hourly.

For the permanently crippled patient, and for those in whom

In the selected cases the aim of the surgeon is to return the extroverted neural structures to the vertebral canal aseptically, effecting also a plastic repair of the deficient posterior spinal muscles and securing closure of the overlying skin. Even when the epithelium is deficient at some part of the sac the application of pinch-grafts may be considered as an immediate post-natal measure, so that a clean field may be provided for later reparative surgery. In such cases it occurs to me that insufflation of sulphanilamide powder, sufficient only to cause a "hoar-frost" appearance, may be an excellent immediate prophylactic measure against infection of the raw surface. We know from our colleagues engaged in plastic surgery that Thiersch or pinch-grafts will take even if applied on top of a layer of sulphanilamide powder.

The defect having been repaired, all may be well There still remains the possibility of hydrocephalus developing later and post-operative follow-up should be maintained for several years at least. There is a well-recognised association between spina bifida and hydrocephalus. The explanation lies in the co-existence, especially in cases of meningo-myelocele, of a deformity of the hind-brain known as the Arnold-Chiari malformation. In normal embryonic development differential growth-rate is accountable for the great disparity in length of the spinal cord and of the vertebral canal. If the lower end of the cord is anchored by abnormal attachment to connective tissues, as growth proceeds the effect is that of continuous traction in the long axis of the cord in a caudal direction So it happens that in the Arnold-Chiari malformation the hind-brain is, so to speak, dragged down into the upper part of the vertebral canal and a pouch-like diverticulum of the fourth ventricle may be found lying dorsal to the cord as far down as the third or fourth cervical segments. It is easy to understand how obstruction to the drainage of ventricular fluid can thus arise. In spina bifida occulta, which constitutes the slightest grade of the abnormality under consideration, the caudal traction effect on the cord is minimal and adolescence may be reached before pes cavus or other deformity of the lower limbs and the onset of disturbance of bladder control raise suspicion that spinal abnormality is present. Some, more fortunate, go through life without developing neurological complications

Post-operative Management

Care of the Bladder.—Normal micturition is interfered with in a high proportion of cases afflicted with disease of the spinal

progress is reviewed, and fitness for discharge discussed This is a good idea and is being taken up elsewhere ; it serves to maintain the interest of all concerned. We find also that we can gain much useful information from the staffs of the therapeutic departments concerning the patient's adaptability, will to recovery, and other important traits of personality, of assistance in planning treatment, and perhaps in advising choice of an alternative occupation

The patient graduates from the school of rehabilitation through the Ministry of Labour Scheme for re-employment of disabled persons, is interviewed personally by a representative from the Labour Bureau, and is thus assisted in finding his feet again in the outside world.

There can be no doubt that circumstances formerly forced us to desert our patients prematurely.

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overdistension of the bladder has been permitted, suprapubic cystostomy gives the best results. Cystostomy is also to be preferred if for some reason the tidal drainage apparatus cannot be provided and catheterisation would be necessary for more than a few days at most.

When the urine is already infected, we have found that instillation of 1 per cent. strength of soluble sulphanilamide solution acts most satisfactorily in cleaning up a septic bladder. About 4 ozs. of the solution is left in the bladder for an hour daily.

General Reconditioning of the Patient

Unwittingly, Hitler has done the spinal cases a good turn. The enormous hospital accommodation which was got ready in anticipation of immediate wholesale bombing has happily enabled us subsequently to make good and constructive use of the beds available in E.M.S hospitals. We are not now obliged by pressure of the waiting list to turn our cases out almost as soon as stitches have been removed from the wound, but can remain in frequent personal contact with the patient in hospital until he is almost at a stage to resume work

Exercises to strengthen the muscles of the back are commenced while the patient is still in bed, on the sixth day or so. He is allowed up on about the tenth day, unless paresis should forbid such early mobilisation, and very soon is performing exercises to promote mobility of the back. He then passes through three grades of physical training, under an Army instructor, while completing his physiotherapeutic treatment. Simultaneously, occupational therapy contributes to the toning-up of muscles and provides the mental stimulus of interesting constructive work. Working a treadle-lathe or weaving-loom, handicrafts of all types, and games of deck-tennis, table-tennis and darts are a few examples of his activities in the occupational therapy department. Some of these developments in post-operative management are new in this country and seem to have required the stimulus and necessities of war to bring them about. In Canada and in parts of the United States, however, those schemes have been in existence for many years and have won the active interest and co-operation of industrial concerns and insurance companies—both, of course, practically interested in the patient's rehabilitation.

Mr Dott has instituted a weekly meeting of the medical and special therapeutic staffs where cases are introduced for treatment,

surface, which occupies a little more than half of the total surface of apposition between the bones, is shaped like an inverted "L," the long limb of which is parallel to the upper margin of the great sciatic notch. The shorter limb of the "L" runs directly upwards from the sciatic notch, approximately level with the posterior gluteal line. The width of the "L" varies with the individual, but, as a rule, measures between half an inch and three-quarters of an inch. Within the bend of the two limbs of the "L" and superior to it there are rough areas both on the sacrum and on the ilium. On both bones these rough areas contain hills and hollows which fit fairly accurately into each other, and

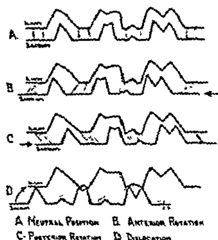


Fig. 1.]

allow about 8° to 10° range of movement (Fig 1, A, B, C). Between these hills and hollows fibres of the interosseous ligament, which binds the bones together, stretch from the sacrum to the ilium Around the joints there are closely applied anterior, posterior, superior and inferior ligaments These are supplemented by the short and long sacro-iliac ligaments on the posterior surface, and by the sacro-tuberous and sacro-spinous ligaments. The part of the joint which is lined by articular cartilage has a synovial lining and is in all respects a true joint It has a fairly generous blood supply and a very generous nerve supply, since it receives fibres from the first, second and third sacral nerves and is closely associated

"SCIATICA"—FROM AN ORTHOPÆDIC POINT OF VIEW

By ROBERT I. STIRLING, F.R.C.S.Ed

THE patients whom one sees complaining of "sciatica," or who are sent with a diagnosis of "sciatica," can be divided into three groups.

The first group contains those who have some disturbance in the joints at the lower end of the spine, or the pelvis, and who have referred pain along one or more of the component parts of the sciatic nerve. No change can be demonstrated in the sensory or motor portions of the sciatic nerve. These are not cases of "true sciatica."

The second group consists of those who have symptoms in the sciatic nerve, which originate from pressure on, or strain or irritation of, the nerve or its roots. The pressure or strain may be caused by congenital or traumatic irregularities, reduction in the size of the intervertebral foramina, or inflammatory changes, or neoplastic growths inside or outside the spinal canal. Usually in such cases there is some alteration in the sensory, if not the motor side of the sciatic nerve. They may be grouped as examples of "symptomatic sciatica," but they are not cases of "true sciatica."

The third group is formed by cases of "true sciatica," *i.e.* interstitial neuritis of the sciatic nerve trunk. This group forms only 5 per cent. of the cases seen. The individual exhibits tenderness and swelling in the nerve trunk and alterations in its sensory and motor distribution.

GROUP 1.—The greatest number of cases in this group are due to a derangement of one of the sacro-iliac joints, but some are due to derangements of the lumbo-sacral joints, and a few are due to disturbances in the joints between the fourth and fifth lumbar vertebræ.

The sacro-iliac joint is an articulation between the ilium and the first three sacral vertebræ, which are fused. In its construction the joint is unique. The cartilage covered articular

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surface, which occupies a little more than half of the total surface of apposition between the bones, is shaped like an inverted "L," the long limb of which is parallel to the upper margin of the great sciatic notch. The shorter limb of the "L" runs directly upwards from the sciatic notch, approximately level with the posterior gluteal line. The width of the "L" varies with the individual, but, as a rule, measures between half an inch and three-quarters of an inch. Within the bend of the two limbs of the "L" and superior to it there are rough areas both on the sacrum and on the ilium. On both bones these rough areas contain hills and hollows which fit fairly accurately into each other, and

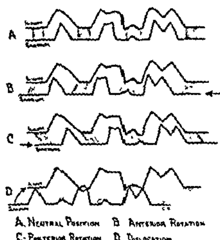


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with the lumbo-sacral trunk arising from the fourth and fifth lumbar nerves. We know that the disturbance of any joint by trauma or infection can cause pain along the other branches of the nerves which provide the nerve supply to the joint. Therefore it is quite understandable that movement in a strained or diseased sacro-iliac joint will elicit referred pain along the segmental distribution of the nerves associated with it. Pain is most commonly referred along the distribution of the first sacral nerve. Occasionally it is referred along the fifth lumbar nerve, and, if the disturbance is situated particularly low down in the joint, the pain may be referred along the third sacral segment, *i.e.* over the ischial tuberosity. The range of movement of the sacro-iliac joint is somewhat increased during the latter months of pregnancy and during parturition. In some cases it seems to be increased during the menstrual period.

A gross *strain* of the *sacro-iliac* joint may be due to severe violence by which the controlling ligaments are torn or stretched, and the hills and hollows, in the non-cartilaginous part of the joint, are overlapped so that the joint surfaces are held apart forcibly (Fig. 1, D). The pain in such cases is excruciating and is usually referred along the sciatic nerve as well as being felt locally. Immediate peace is secured by manipulative replacement. The more common sacro-iliac strain, however, does not follow severe trauma, but is due to the effects of bad posture accentuated by a comparatively trivial injury, such as catching the heel on a step while descending a stair, or by a sudden muscular effort as in lifting a heavy suitcase.

When an individual maintains a good posture the sacro-iliac joint, like other joints, is in a position of neutrality, *i.e.* no set of ligaments is taking an undue or continued strain. If, however, the muscles are unable to maintain a good posture a prolonged strain is thrown either on the anterior or posterior ligaments, which become stretched, while the opposing ligaments become contracted. The joint thus develops definite adhesions which limit its action. It is in such circumstances that a small trauma, which in the normal way would merely put the joint through its full range of movement, strains the adhesions and brings about local and often referred pain. If the joint is left in a position of strain with adhesions, over a long period, the cartilage is replaced by fibrous tissue and the joint becomes largely non-functioning. This change may come as a normal process with increasing age.

The lumbo-sacral joints and the joints between the fourth and the fifth lumbar vertebræ can also be affected in the way I have described, and the referred pain is of a similar nature.

The differential diagnosis between lumbo-sacral and sacro-iliac referred pain is made by moving the respective joints and reproducing the pain by such movements. The examination should be carried out first with the patient standing; second, with the patient sitting; and third, with the patient lying down. There is obviously no time to give a description of a full examination, which requires the best part of half an hour. The main points, in so far as they refer to sciatic pain, can be stated briefly:—

(1) With the patient standing a careful inspection is made. A scoliosis may or may not be present, but it usually becomes evident when the patient is asked to bend forward to touch his toes, keeping the knees straight In the case of sacro-iliac joint trouble it is seen that the lumbar spine moves evenly and fully until it is in complete flexion, and that the pelvis tilts—as a whole—until a pull is put upon the flexor muscles of the knee which arise from the ischial tuberosity. The patient then stops bending, or flexes the knee on the affected side because he feels referred pain down the leg. Since the patient has an affected sacro-iliac joint no pain will be felt while the pelvis tilts *as a whole*, but as soon as the innominate bones have to stretch the hamstrings, in order to tilt forward, it is necessary that the sacrum should rotate forwards so that the flexion force can be transmitted through the sacro-iliac joints to the innominate bones As this requires movement at the sacro-iliac joints the patient immediately feels referred pain When the disturbance is in the lumbo-sacral joints and the individual bends forward, the lumbo-sacral joints, and usually the fourth and fifth lumbar joints, are held absolutely rigid.

(2) When the patient is sitting down, if he has *sacro-iliac joint strain*, he can touch his toes without any referred pain because the bending of the knees slackens off the flexor muscles and allows the pelvis to tilt without any movement at the sacro-iliac joints The individual with lumbo-sacral strain, however, usually has referred pain because the lower part of the spine must still be held

rigid, and, unless the other joints are sufficiently lax to allow the individual to touch his toes, the affected lumbo-sacral joints will have strain put upon them.

(3) When the patient is in recumbency, the chief test is the straight leg raising test. Others, such as rotation to put torsion on the lumbar spine and sacro-iliac joints, and the application of lateral pressure are also valuable.

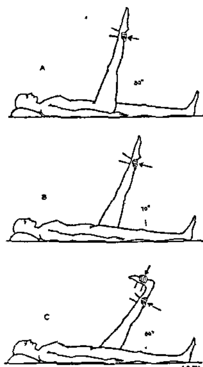


FIG. 2

To clarify the mechanism of the straight leg raising test, let us presume that the individual has an affected left sacro-iliac joint (Fig 2, A). With the patient lying perfectly supine, the right leg is raised with the knee straight and the foot pointed, and the raising is continued until the individual complains of pain. Occasionally this pain is first felt behind the right knee, but the examination should not stop there. The leg should be pushed further up, when the pain will be found to pass down the *left* leg. Probably the right leg will be raised to 80°. It will be seen that in the

first stage the movement takes place entirely in the hip joint, but, when the flexors of the knee are tightened and a pull is put on the ischial tuberosity, the upper part of the ilium on the right side is rotated backwards—the movement taking place at the right sacro-iliac joint. This movement can continue for 10° or so. Further movement of the leg upwards is then permitted only by tilting the sacrum. This, however, entails movement in the left sacro-iliac joint, *i.e.* the sacrum is rotated backwards while the left ilium lags behind. Movement being thus forced upon the affected left sacro-iliac joint, referred pain is experienced down the sciatic distribution on the left side. The right leg is lowered and the left leg is raised in turn (Fig. 2, B), and, if there is no additional complicating factor, it will be possible to raise it to about 70° before the referred pain is felt down the left leg, that is as soon as the left sacro-iliac joint begins to be moved. If the left leg is now dropped down a matter of 10° until the referred pain has gone entirely and the foot, which was plantar flexed, is dorsiflexed (Fig. 2, C), there will be a return of the pain if there is any neuritis in the nerve or fixation of the nerve roots, because this movement stretches the posterior tibial nerve and through it the sciatic nerve. If, however, there is no complicating factor in the sacro-iliac strain there will be no pain.

When the straight leg raising test is applied to a patient with lumbo-sacral joint strain it will be noted that pain will be experienced as soon as the lumbo-sacral joints move, *i e.* as soon as the sacrum begins to rotate backwards It is obvious that the sacrum will be made to rotate when the legs are raised to the same level.

I have stated that the chief causes of strain of these joints are faulty posture and trauma The *faulty posture may be due* to congenital defects, for example, congenital dislocation of the hips, or congenital tightness of the ilio-tibial tract, or tropism of the lower lumbar joints, or to acquired conditions which upset the alignment of the pelvis, such as badly set fractures of the leg, or abnormal fixation of the hip joint by arthritis, but it is more commonly caused by over-tiredness, obesity, or general slackness of the musculature of the individuals The traumatic causes of

strain, apart from falls, accidents, and the like, are most commonly found after the vigorous assumption of the lithotomy position for operations, and following childbirth. After childbirth there is, occasionally, not only a sacro-iliac strain but an apparent damage to the sciatic nerve. This may be produced by pressure from the fœtal head. The result is a transient paralysis, usually limited to the peroneal distribution.

GROUP 2. This group presents by far the most puzzling problems. In the vast majority of cases some alteration is brought about by the pressure on, or stretching of, or interference with the nerve roots, or the nerve itself, and therefore there is usually not only some loss of musculature, which varies with the part of the nerve affected, but there is some sensory disturbance and not infrequently a loss of the ankle jerk. Again, as with the first group, the referred pain is usually along the line of the fifth lumbar or first sacral nerve distribution, *i.e.* the area to the outer anterior and slightly posterior aspect of the leg and the lateral part of the foot. Occasionally, it is apparent in the cleft between the first and second toes. There may be complete anæsthesia, lack of appreciation of sharp or blunt points, failure to distinguish between heat and cold or between divider points, and loss of position sense of the small toe. Occasionally there is hyperæsthesia.

The main causal factors are :—

(1) Static arthritis or osteo-arthritis of the sacro-iliac joints or lumbo-sacral joints.
(2) Sacralisation of the fifth lumbar transverse process.
(3) Spondylolisthesis
(4) Infections or tumours abutting the lumbo-sacral or sacro-iliac joints
(5) Radiculitis.
(6) Prolapse of the *nucleus pulposus* and thickening of the ligamentum flavum.
(7) Tumours or inflammation in the spinal canal.
(8) Tumours or inflammation outside the spinal canal.
(9) Fibrositis

(1) By *static arthritis* one means the changes occurring in a joint which has been subjected to strain in an incorrect weight bearing line. When such a strain is protracted the joint becomes worn like a badly hung gate, with osteophytes growing at its periphery. As has been stated, a faulty posture causes strain

in the low lumbar and pelvic joints. If this strain continues for a long period static arthritis will develop. In the lumbar region the osteophytic growth at the periphery of the joints may encroach upon the intervertebral foramina to such an extent that the nerves passing through them will be interfered with, or the nerve sheaths become adherent by being caught up in the non-septic inflammatory reactive swelling round the joints. Apart from poor posture, produced by congenital deformities or by the factors we have already mentioned, static arthritis may be brought about by the disappearance or atrophy of an intervertebral disc, without there being necessarily any protrusion of the nucleus pulposus. It also follows unreduced fractures or pathological collapses in other areas of the spine.

Osteoarthritis developing in the intervertebral facets may have the same effects as static arthritis, and the same symptoms frequently accompany the early stage of spondylitis ankylopœtica, local Paget's disease and osteomalacia

(2) In *sacralisation* of the fifth lumbar transverse process the anterior branch of the fourth lumbar nerve runs in front of the abnormal transverse process. If the patient assumes a faulty posture, with tilting forward of the sacrum and the fifth lumbar vertebra which must accompany it, there will be a pull forwards *on the anterior branch of the fourth nerve as it goes to join the* fifth. This usually results in a straining of the fifth lumbar nerve and sometimes in a straining of the first sacral nerve as well. For some unexplained reason the fourth nerve usually seems to escape trauma, or, at any rate, it fails to manifest untoward symptoms. In certain gross cases, the space below the abnormal transverse process may be so narrowed that the normal clearance of the fifth nerve is definitely encroached upon to the detriment of the nerve Very occasionally a pseudo-articulation forming between the abnormal transverse process and the sacrum or the ilium becomes the site of arthritis. The pain which is experienced may then be of a referred nature

(3) *Spondylolisthesis* These cases are due to defects in the ossification of the affected vertebra. The failure of fusion usually lies between the upper and lower facets The body with the upper facet tends to slip forward with age, but the process may be accelerated by trauma Once the slip has started it will tend to drag on the adjacent nerves—usually the fourth or fifth lumbar nerves.

(4) Infections or tumours abutting the sacro-iliac joints.

Patients occasionally report with no local symptoms near the joints, but complain of "sciatica." One has seen such cases with tuberculosis of the ilium and with a giant-cell tumour of the sacrum abutting the sacro-iliac joint. These cases illustrate the immense importance of securing good radiographs of all patients suffering from sciatica.

(5) *Radiculitis.* In this condition there seems to be a binding down of the sheaths or of the roots of the nerve in the area of their entrance into the intervertebral foramina. In the majority of cases it is impossible to demonstrate any local infection by examination of the cerebro-spinal fluid, although this usually shows an increase in protein and may even show an increase in the number of cells. When radiculitis is present there is, however, usually some definite source of sepsis in the individual. When the area is explored adhesions of the nerve sheath are found round the foramen and sometimes the nerve roots are red and inflamed. On making a clinical examination of such a case one generally causes pain when dorsiflexing the foot in the straight leg raising test (Fig. 2, C). A similar pain is elicited by bending the head forcibly forward on the chest. In the first test obviously the nerve is pulled downwards from the adherent or irritated area, and in the second the spinal cord is pulled upwards away from the affected area. Frequently there are sensory or muscular changes

(6) *Prolapse of nucleus pulposus.* This condition is being more and more widely recognised as a common cause of pain in the line of the sciatic nerve. The nucleus pulposus, which is a remnant of the notochord, consists of a gelatinous but rather stringy mass in the centre of the intervertebral disc. Usually as the result of trauma the outer posterior margin of the disc is ruptured, and the nucleus pulposus is pushed outwards through the rupture in the disc or into the weakened edge of the disc. This protrusion is, of course, separated from the linings of the cord by the posterior longitudinal ligament (Fig 3). The symptoms it brings about depend largely on the size and situation of the protrusion If the protrusion is very near a foramen it may press hard upon a single nerve, even though the protrusion is a comparatively small one If, on the other hand, the protrusion is large and more centrally placed, it may affect several nerves in the cauda equina The most common situations for the protrusion of the nucleus pulposus are between the fourth and fifth lumbar and the fifth lumbar and first sacral vertebræ. Nature's cure is

to reverse the curve in the lumbar area to give the maximal space in the lumbar canal and intervertebral foramina, and so in a well-established case the patients always present a very flat or even convex lumbar spine. Scoliosis is usually present if the protrusion is towards one side, and the scoliosis is away from the affected side. There is frequently tenderness over the sciatic nerve at the inferior margin of the glutæus maximus; there is a loss of ankle jerk; and a loss of sensation usually on the antero-lateral aspect of the leg and the lateral part of the foot. Occasion-

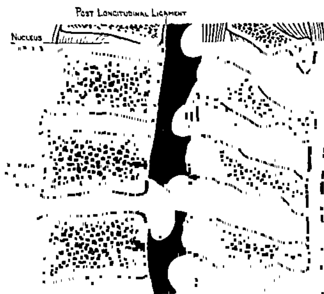


Fig. 3.

ally a muscular weakness in the peroneal muscles of the dorsi-flexors of the foot may be the first sign Lumbar puncture sometimes shows an increase of protein in the cerebro-spinal fluid The increase seems to be proportional to the amount of root irritation present Individuals suffering from this condition have usually definite periods of remission as distinct from spinal tumours or infective lesions in the canal. Intrathecal injection of lipiodol shows up the condition very clearly, but this procedure is becoming less frequently applied because, following the injection of the poppy oil, more and more cases exhibiting untoward symptoms are being reported. Aerography of the spinal canal

is an alternative method which is sometimes used. While it is highly successful in the upper reaches of the spine, in the lowest lumbar and lumbo-sacral areas it is usually disappointing, except on very thin subjects with large protrusions.

The ligamentum flavum, which runs between the contiguous laminæ and abuts the intervertebral foramina, is sometimes pathologically thickened so that it encroaches upon a foramen and may press upon the emerging spinal nerve (Fig. 3). It is often impossible to distinguish clinically between a protrusion of the nucleus pulposus and a thickening of the ligamentum flavum.

(7) *Tumours in the spinal* canal may arise from the vertebræ, the meninges, the nerve roots, or in the cord itself. In the early stages the symptoms may be difficult to differentiate from those of a nucleus pulposus protrusion, but they are usually much more persistent and progressive. Froin's syndrome may be present and Queckenstedt's test may be positive. These are almost unknown in a case of protrusion of the nucleus pulposus.

(8) Tumours, which affect the sciatic nerve outside the spinal canal, are usually bony and arise from the vertebræ, the pelvis, or the femur, and can be easily recognised by radiography. Less commonly they arise from the pelvic viscera, *e.g.* a calcified fibroid, or from the genito-urinary or alimentary tracts. They may be simple or malignant in character. Occasionally the tumour is in the sciatic nerve itself.

(9) *Fibrositis* in the glutæus maximus and other muscles closely associated with the sciatic nerve may cause symptoms in the nerve. Of these muscles the most interesting is the piriformis muscle. Normally, this muscle arises from the sacrum between and lateral to the foramina through which the anterior sacral nerves emerge. Many exceptions to this rule have been described. The muscle may arise from the sacrum medial to the foramina, in which case the first three sacral nerves pass through the muscle to join the lumbo-sacral trunk. Sometimes the sciatic nerve lies behind the muscle; sometimes it is in front; sometimes the muscle divides to let the nerve through; sometimes the nerve divides to let the muscle through. Obviously fibrositis, or myositis, in the muscle may affect the sciatic nerve in many ways, just as similar affections of the scalenus medius muscle affect the long thoracic nerve in a stiff neck. A gross case can be appreciated by high rectal examination.

GROUP 3. In cases of "true sciatica" there is almost certainly

an infective factor in the body, and a most careful examination has to be made for it so that it can be eliminated. Probably the most common sites are in the teeth, naso-pharynx, gall bladder, large bowel, and the genito-urinary system; but metallic poisoning and an abnormal carbohydrate metabolism must not be forgotten. The active signs of "sciatica" may be protean but the pain is persistent. The nerve is tender and swollen and there is always some sign of interference with its conductivity.

Treatment.

The treatment, of course, varies with the condition that is causing the pain. Unfortunately, entirely simple cases are rare, there are usually certain complications. For example, an individual with a chronic strain of the sacro-iliac joint very soon develops gross fibrositis in the muscles around that joint, and the treatment of the case involves not only restoring movement to the joint but also re-educating the muscles, after the fibrositis has been eliminated. Or again, an individual who has a nucleus pulposus protrusion with symptoms of long standing, develops a strain of the lumbar and pelvic joints and may even develop static arthritis in these joints. No matter how simple the causal factor may be the presence of septic foci may, and usually does, produce further complications, so in every case the throat and rectum have to be examined and the terrain between has to be overhauled. It will be appreciated, therefore, that in the treatment of every case, in the various groups described, septic foci must be eliminated, and, no matter what other treatment is given, before the patient is dismissed he must have his posture correctly restored. If these two elementary rules are not observed relapses are bound to be frequent A chronic strain will not settle down in the presence of sepsis, and until a good posture is obtained a strain will persist even after sepsis is eliminated.

GROUP I Sacro-iliac strain. Manipulation of the joint to break down adhesions, and restoration of the musculature with the assumption of the proper posture is the rule in most cases. In a chronic case the patient cannot be treated adequately as an out-patient. In-patient treatment from a fortnight to three weeks is required at the very least. Patients should be nursed on a hard bed; should have fomentations for twenty-four hours, following the manipulation, should then have massage to eliminate the thickening round the joint and the fibrositis present

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The treatment, of course, varies with the condition that is causing the pain. Unfortunately, entirely simple cases are rare ; there are usually certain complications. For example, an individual with a chronic strain of the sacro-iliac joint very soon develops gross fibrositis in the muscles around that joint, and the treatment of the case involves not only restoring movement to the joint but also re-educating the muscles, after the fibrositis has been eliminated. Or again, an individual who has a nucleus pulposus protrusion with symptoms of long standing, develops a strain of the lumbar and pelvic joints and may even develop static arthritis in these joints. No matter how simple the causal factor may be the presence of septic foci may, and usually does, produce further complications, so in every case the throat and rectum have to be examined and the terrain between has to be overhauled. It will be appreciated, therefore, that in the treatment of every case, in the various groups described, septic foci must be eliminated, and, no matter what other treatment is given, before the patient is dismissed he must have his posture correctly restored. If these two elementary rules are not observed relapses are bound to be frequent. A chronic strain will not settle down in the presence of sepsis, and until a good posture is obtained a strain will persist even after sepsis is eliminated

GROUP 1. Sacro-iliac strain. Manipulation of the joint to break down adhesions, and restoration of the musculature with the assumption of the proper posture is the rule in most cases. In a chronic case the patient cannot be treated adequately as an out-patient. In-patient treatment from a fortnight to three weeks is required at the very least. Patients should be nursed on a hard bed , should have fomentations for twenty-four hours, following the manipulation , should then have massage to eliminate the thickening round the joint and the fibrositis present

in the large muscles controlling the joint, and graded exercises should be carried out frequently during the day until the patient is able to get up more and more. The time up must, of necessity, vary with the patient, and is controlled entirely by the length of time the patient can hold the proper attitude while standing, walking, or sitting. In the grosser cases a brace may have to be worn, or the joint may have to be fused, but the vast majority should be treated by manipulation at first.

Strain of the lumbo-sacral joint is similarly treated with manipulation, but if the strain is of longer duration, and there are some changes in the joints, the temporary wearing of a brace is of inestimable value.

Congenital or acquired conditions causing strain on the sacro-iliac and low lumbar joints must be rectified, if possible. Dislocated hips should be replaced or bifurcation operations carried out, or in the case of congenital tight ilio-tibial bands, these should be sectioned across as a preliminary to postural exercises. Osteotomies may have to be performed on the femur or leg bones before a good weight-bearing posture is possible.

GROUP 2. (1) Static arthritis. Treatment here should consist of restoring proper posture so that the weight of the body falls in the correct line on the affected joints. Usually, if the joints are mobilised and the muscles are developed, a correct weight-bearing posture will result. Occasionally, rest in a plaster shell and the wearing of a brace is necessary, and if even this proves ineffective a local fusion may have to be carried out.

(2) Sacralisation. The condition is a congenital one and yet seldom causes symptoms until the patients are over thirty years of age, that is until the resiliency of youth is passing and the posture is apt to become poor. Consequently, the restoration of a correct posture and the temporary wearing of a brace will cure most cases. In persistent cases removal of the abnormal process may have to be carried out.

(3) Spondylolisthesis. Most of the early cases do very well with physiotherapy, with the strengthening of the muscles and occasionally the wearing of a brace. If the symptoms persist, however, or the slip is seen to be increasing, a fusion of the part is indicated The fusion can be carried out either from behind or in front. Most cases do very well with posterior fusion, which is much less shock-producing than the anterior approach. Possibly the only indication for the anterior approach is if there is a defect

in the lower lumbar or sacral vertebræ which prohibits an adequate fusion at the back.

(4) Infections or tumours abutting the lumbo-sacral or sacro-iliac joints should be dealt with on general lines.

(5) Radiculitis. Treatment of this condition consists of loosening the adherent nerve sheaths at the intervertebral foramina This can be done in some cases by forcibly flexing the straight leg at the hip, under anæsthesia, to stretch the sciatic nerve. An alternative method is an epidural injection by which saline is injected into the epidural space. As the separation is taking place the individual has acute pain in the sciatic nerve, such as he experienced before. In gross cases an operative release in the area may have to be carried out with or without section of the posterior nerve roots. When carrying out the epidural injection it is advisable to put in a local anæsthetic to anæsthetise the part and make it possible to manipulate the sacro-iliac joint and stretch the leg. This is indicated because, if the case of radiculitis has persisted for any length of time, there is almost certain to be a stiffening of the joints and thickening of the ligaments

(6) Prolapse of the nucleus pulposus and thickening of the ligamentum flavum. As we have seen, nature's method of dealing with this condition is to produce a reverse lumbar curve. In a very large number of cases of prolapse of the disc and of ligamentum flavum thickening, if the individual has still a lordosis, a relief of symptoms, which may persist for years, can be obtained by improving the posture until the lordosis has been obliterated and indeed until an almost straight lumbar spine has been achieved. It is a wise rule that every orthopædic procedure should be carried out to try to relieve this condition before one has recourse to operation Even if operation has to be carried out in the end the preliminary limbering up curtails convalescence considerably

It is sometimes exceedingly difficult to differentiate between a prolapse of the nucleus pulposus and a thickened ligamentum flavum on the one hand and radiculitis on the other. Considerable help is sometimes obtained by giving an epidural injection, because, as the fluid is inserted, frequently one can tell whether the pain produced is due to radiculitis or a nuclear prolapse. In the former case, if adhesions separate, the pain is relieved. In the latter, the pain is more apt to persist. One takes it as a rule that if the symptoms are those of a nucleus pulposus, as I

have described them, and if an epidural injection and postural correction does not bring about relief the case should be explored forthwith without having recourse to lipiodol injection. Formerly the operation was rather a formidable one, necessitating the laminectomy of several vertebræ, opening of the dura, and finally bone-grafting. Now, however, it has been found possible to remove the nucleus pulposus through the gap between contiguous laminæ, without removal of any bone. Occasionally, a small portion of bone may have to be removed from the upper or lower lamina, but even a hemi-laminectomy is unnecessary. During this approach the ligamentum flavum has to be removed *in toto*, and therefore if it is responsible for the symptoms the operation will have been successful.

(7) Tumours and infections inside the spinal canal. These have to be investigated and dealt with in the normal way.

(8) Tumours outside the spinal canal of whatever origin should be removed or irradiated according to their nature.

(9) Fibrositis in muscles is usually treated by removal of sepsis, the application of local heat and massage, the ingestion of alkalis and occasionally by the injection of a local anæsthetic, and always by muscle re-education. In menopausal cases progynon, or its equivalent, may be required. If the condition is very acute, however, rest for ten days in a plaster shell will often prove to be very beneficial. Needless to say, massage of the piriformis muscle is out of the question. Section of the piriformis tendon has been suggested. I have only seen two cases of the condition and both settled down with rest and alkalisation.

GROUP 3 True sciatica should be treated by rest until the acute symptoms have subsided. The rest may be given by weight traction of eight or ten pounds, or in severe cases by the application of a plaster-of-Paris spica. Medication by vitamin B seems to be of doubtful value. When the condition has settled down muscle re-education must be undertaken. Occasionally adhesions form in the nerve, but usually these are severe only in cases where rest has not been instituted. When adhesions are present the nerve should be stretched under an anæsthetic and the stretching should be followed by a course of physiotherapy. The injection of a saline solution into the nerve trunk may serve the same purpose as the stretching, but I have found the results much less certain. The injection of the nerve with potent local anæsthetics is usually disappointing and may be dangerous.

To sum up briefly, the diagnosis and treatment of cases

included under the groups of "sciatica" normally follow these lines:—

(1) A complete history has to be taken.
(2) The patient must be inspected and the movements of certain of his joints carefully examined and the findings assessed.
(3) The sensory appreciation, reflexes, and the condition of the muscles must be noted
(4) All sources of sepsis must be sought and eradicated.
(5) Good radiographs of the lumbar spine, pelvis, and hips must be secured
(6) A pelvic examination has to be made.

If the joints, or extra-spinal agents, are held to be the cause of the condition the appropriate treatment, as described, is instituted. If they are not considered to be responsible the condition will be due to true sciatica—radiculitis—prolapse of a nucleus pulposus—thickening of the ligamentum flavum—or a spinal tumour. True sciatica should be treated initially by rest. With regard to the others, unless the examination of the cerebro-spinal fluid suggests the presence of a tumour, they should be treated by an epidural injection, and physiotherapy should be commenced in the first place

It cannot be over-emphasised, however, that, whatever may have been the original cause of the trouble, until the patient has been restored to a good posture the treatment of his case is not complete.

ACUTE INTESTINAL OBSTRUCTION FROM THE CLINICAL STANDPOINT

By K. PATERSON BROWN, F.R.C.S.Ed
Surgeon, Royal Infirmary, Edinburgh

THE subject of intestinal obstruction may appear to be somewhat hackneyed. It has been discussed repeatedly, hundreds of papers have been written regarding it, but in spite of all this investigation there still remain many problems requiring solution. *Furthermore, intestinal obstruction is still amongst the most* serious of the abdominal emergencies, but there is no doubt that in those clinics where this condition has been intensively studied results show very definite improvement.

It is impossible with the time at my disposal to do more than touch briefly on certain aspects of the subject, and I shall make no attempt to prove or disprove the theories which have been advanced in explanation of the high mortality. Rather I would endeavour to place before you certain physiological facts and discuss how the physiology is modified by various forms of intestinal obstruction in the small bowel, and so be in a position to describe a rational form of treatment based on these facts. I *propose to consider only those cases which may* be grouped under the heading of post-operative obstruction.

Such obstructions are usually the result of adhesions, peritonitis or a combination of the two. Those due to adhesions may develop soon after the abdominal exploration or may be long delayed. In the former case the obstruction tends to be of the simple mechanical type, but if a considerable time has elapsed before acute symptoms develop, there is a greater likelihood of a strangulation being present. When peritoneal infection is the primary cause we have to deal with that dangerous condition, paralytic ileus

Simple Mechanical Obstruction. — The small intestine may be obstructed by a single band or perhaps more commonly as a result of the matting together of numerous segments of bowel. The effects will vary with the site of the lesion; if it be situated high in the jejunum the digestive juices cannot reach the absorptive areas of the intestine, rapid distension results and

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intestinal colic and copious vomiting are early features. Obstructions of the lower ileum present a different picture; the digestive secretions do reach the jejunum and ileum and absorption is possible, but in such cases it is incomplete and there is a gradually increasing distension of the bowel. This distension produces certain reflex and local changes; an increase in the secretion from the intestinal glands, a venous stasis in the bowel wall which becomes œdematous, and eventually a state of ileus may be superimposed upon the mechanical obstruction with a reactionary effusion into the peritoneal cavity. In many cases reflex vomiting occurs early, but it is perhaps not sufficiently appreciated that not a few patients do not vomit until gross distension has developed. It is evident that in both types of obstruction there is a common factor—loss of water. In the high obstruction this loss is the result of vomiting and is very obvious; in the low obstruction, although there may be no vomiting, loss of water still occurs but is concealed as it lies stagnant and useless in the distended intestine, in the œdematous bowel wall and in the peritoneal cavity. A similar loss will occur in the distended bowel of a paralytic ileus. Here then, in dehydration, we find one of the essential effects of acute intestinal obstruction. The term dehydration is familiar to everyone, but is it always realised what the term means in actual volume of water lost? A patient suffering from serious dehydration has lost at least 6 per cent. of his body weight in water alone. There is a second effect closely associated with dehydration. In the presence of a high obstruction, chloride ions in the gastric juice are lost by vomiting and there is a consequent fall in the concentration of chlorides in the extracellular fluid. To maintain the total electrolyte content of that fluid there is an increase in the concentration of bicarbonate which takes the place of the lost chlorides. The sodium which has been set free must be conserved by the body if extracellular fluid volume is to be maintained and it unites with the bicarbonate. As a result of these changes there is an increase in the CO_2-combining power of the blood, a fall in the plasma chloride concentration, and a state of alkalosis exists.

Falconer and Lyall have shown that there is also a loss of potassium, which is the main basic salt of intracellular fluid. It is believed that this loss is mainly the result of vomiting or of gastric aspiration, as the gastric secretions alone contain a high content of potassium. Further reference will be made to this when fluid therapy is discussed.

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Requirements of Electrolytes.—Sodium chloride is the principal salt which the body requires, and a satisfactory salt intake is about 6 gms. daily. If in a normal person salt is withheld, its excretion in the urine steadily diminishes during the first few days, but the plasma chloride remains normal. If, however, the salt intake is stopped, and in addition there is a serious loss of sodium chloride by vomiting, from intestinal fistulæ or peritonitis, the plasma chloride concentration falls below the normal of 560 to 650 mgs. per 100 c.c. and a state of hypochloræmia exists. Falconer and Lyall recommend that from 15 to 20 gms. of sodium chloride are required for every 100 mg. that the plasma chloride is below normal. Thus a patient whose plasma chloride concentration stands at 400 mgs. requires about 40 gms. of salt

Every patient suffering from acute intestinal obstruction will show to a varying degree signs of dehydration and hypochloræmia, and these must be corrected if treatment is to be successful. Fortunately, normal saline will supply both water and salt, so at one and the same time the lost electrolytes can be replaced and the dehydration improved. It may well be that the salt depletion is corrected before an adequate amount of water has been given to stabilise the water balance. Here lies a practical danger. If the total amount of water required is given in the form of saline, the patient will receive a very considerable excess of salt and serious consequences may result. When large amounts of salt are given in excess of requirements they cannot be eliminated in the urine and both salt and water are retained. The excess of sodium in the extracellular fluid will, by raising its osmotic pressure, result in the transference of more water into the extracellular fluid, and that in turn leads to clinical œdema with all the dangers which that entails. In order to prevent this complication it is most important, when salt depletion has been corrected but more water is required to control dehydration, to give it in the form of 5 per cent. glucose solution in *distilled water*. The administration of hypertonic saline is often recommended as a rapid and easy way to replace chloride deficiency, but such a procedure is not only ineffective but actually dangerous. Hypertonic saline supplies an excess of salt without a balancing quantity of water, with the result that dehydration is actually increased. Some years ago I had a fatality immediately following upon the giving of hypertonic saline, and I know of three other similar cases. It must be remembered that although loss of chloride causes a fall in the plasma chloride concentration, excessive salt

In the presence of an obstruction low in the intestine somewhat similar changes may take place, especially if vomiting is a feature, but chloride loss is more variable although the intestinal secretions are rich in chlorides. Instead of an alkalosis the patient may be in a state of acidosis, associated with an inadequate intake of water and glucose. The glycogen reserve of the liver becomes depleted, so that body fats have to be utilised, and as they cannot be completely oxidised in the absence of carbohydrate, ketosis results. This is particularly liable to occur in children whose power to store carbohydrate in the liver is limited. While the various changes described are of common occurrence, it must be admitted that considerable variations are met with. Falconer and Lyall state that no uniformity characterises the biochemical changes in the blood produced by obstructions at any given level of the small intestine. Such a statement must not be taken to mean that treatment directed towards combating these changes is purely experimental; there is abundant clinical evidence of its value. It is not suggested that a disturbance of water and salt balance is the only factor which militates against recovery in acute intestinal obstruction, but there can be little doubt about the importance of the rôle which it plays. If, therefore, treatment is to be placed on a rational basis, there must be a clear understanding of the amounts of water and salt that are required to maintain normal metabolism.

Requirements of Water.—This problem has been very fully investigated by Maddock and Coller, and by Bingham and Bartlett. Their findings will be very briefly summarised. Under normal conditions an individual loses daily from 1000 to 1500 c.c. of water in vaporisation from the *skin* and *lungs*, a small amount in the fæces, and 600 to 1500 c.c. in urine. Thus 1750 to 3200 c.c. of water is required daily in order to maintain a correct water balance In health about 1500 c.c of water is obtained from an ordinary diet apart from any that may be drunk, but in surgical patients, during what may be termed the operative phase, this fluid from the diet is not available. It has been estimated that a surgical patient requires about 2000 c.c. of water daily, together with 1500 c.c. for the urine, making a total of 3500 c c. If this fluid need is not met, dehydration results. It is evident that in special circumstances, such as arise in the presence of an intestinal obstruction, very large quantities of water may be lost, and these abnormal losses must be replaced in addition to the daily allowance of 3500 c c.

and continuing it for forty-eight hours. I firmly believe, though it is not capable of proof, that this procedure may abort a threatened ileus. There is no place for pituitrin or intestinal stimulation of any kind once an ileus exists, and therefore I do not employ it when a peritonitis is already well established. In such cases intestinal decompression with rest to the bowel is the correct procedure. Morphine, $\frac{1}{6}$ gr., should be given sufficiently often to ensure to the patient complete rest and freedom from discomfort. Admittedly morphia is an intestinal stimulant, but its action is to maintain bowel tonus rather than to produce active peristalsis. I believe that continuous suction is equally necessary for those patients in whom the continuity of the bowel has been temporarily interrupted, as for example when resection of intestine or an entero-anastomosis has been necessary. It is very doubtful if the reconstituted intestinal tract is immediately capable of transmitting its contents, especially if the proximal bowel is grossly distended. Under such circumstances an indwelling duodenal tube with suction should be employed for forty-eight hours.

Gastro-duodenal Aspiration.—In 1884 Kussmaul and Cahn used a stomach tube for gastric decompression, and they reported that such treatment diminished the size of the intestine, the intra-abdominal pressure, and reduced violent peristalsis. It was not until 1925 that continuous suction through a duodenal tube was employed in the treatment of peritonitis, and the possibilities of this form of treatment were not fully realised until 1931. We owe a great deal to Wangensteen, Paine and their co-workers for the successful application of this procedure to the treatment of intestinal obstruction. Gastric intubation of a patient who has a distended stomach and is vomiting, presents certain difficulties. A nervous patient in poor condition may be considerably upset, and it is most important therefore that an explanation be given of what it is proposed to do and of the increased comfort which is likely to follow the introduction of the tube. Occasionally, a patient is quite unable to swallow the tube, and in such a case the spraying of the fauces with cocaine will be found to facilitate matters. The tube is best introduced through the nares, but if this proves to be difficult it must be passed through the mouth which, though less comfortable, is well tolerated. If gastric suction is all that is required, I prefer to use a No 12 œsophageal tube, but if duodenal intubation is desired a special heavy tipped tube with several perforations is employed. In my experience the ordinary Ryle's tube is often unsatisfactory

administration and retention do not give rise to a plasma concentration figure above the normal, therefore it cannot be used as a guide to excessive salt intake. I have already referred to the loss of potassium which may occur in high intestinal obstruction, and to correct this it has been suggested that Ringer's solution should be given instead of saline. The former solution contains a small amount of potassium and, on theoretical grounds, there is the added advantage that it is less likely to give rise to clinical œdema.

We are now in a position to consider the treatment of acute intestinal obstruction, and I propose in the first place to refer to conservative measures. These are employed essentially in the treatment of paralytic ileus, and I will digress for a moment to discuss some of its clinical features. This form of obstruction occurs most commonly following a peritonitis, but may develop after any abdominal operation apart altogether from infection. It is not infrequently associated with extra-abdominal lesions, notably spinal fractures. In such cases the ileus usually develops after the spine has been manipulated and the plaster case applied. I have seen three examples of this condition in the past six months, and in each case the patient required intensive treatment by the methods to be described Following operation, ileus develops insidiously, there is a gradual and progressive distension of the abdomen, associated with an effortless type of vomiting, whereby the patient loses very large quantities of fluid, and unless steps are taken to prevent it, the sunken, pinched cheeks, the dry tongue, the intense thirst, and the low urinary output soon demonstrate the establishment of dehydration. There is a complete absence of intestinal colic, and examination reveals a painless, distended and perfectly quiet abdomen, in marked contrast to the abdomen of the patient with a mechanical obstruction, when vigorous intestinal peristalsis causes severe colic, and borborygmi are easily detected with the stethoscope. Differentiation from a mechanical obstruction is of vital importance, as the treatment of paralytic ileus is conservative while that of a dynamic obstruction is usually operative

Treatment.—Experience has taught us in what type of case a paralytic ileus is to be looked for, and so steps can be taken at an early stage in an endeavour to prevent its occurrence. For many years it has been my custom, in such cases as gangrenous appendicitis with early peritonitis, to administer pituitrin, 1 c.c. at four-hourly intervals, commencing immediately after operation

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distended. The perforation was sutured, drainage established, and the abdomen closed. Post-operatively continuous suction was commenced and had to be maintained for five days; large amounts of dark, foul material were removed for the first three or four days. During this time an adequate urinary output was achieved, 9000 c.c. of fluid being given in the first twenty-four hours. The amount of fluid lost by gastric aspiration was carefully charted, and with this information and the knowledge of the amount of fluid normally required, the correct fluid balance was established and maintained by intravenous saline and isotonic glucose solution. At one stage a rise in respiratory rate caused added anxiety, but this was checked by giving M. & B. 693 with the drip infusion. On the sixth day the gastro-duodenal suction was stopped, as the abdominal distension had been reduced and the aspirated material was no longer foul-smelling. No further vomiting occurred, but as the patient did not take sufficient fluid by mouth, the intravenous drip was continued for a further three days. On the tenth day the bowels moved spontaneously, and thereafter there was a slow but uninterrupted recovery. Although a successful result was obtained in this case, it will be realised that in the presence of a peritonitis, gastro-duodenal aspiration only assists towards recovery by removing the added burden of intestinal obstruction from a patient fighting against infection.

We may now consider whether or not it is justifiable to treat mechanical obstruction by conservative measures. Under no circumstances may a strangulation obstruction be treated by intestinal decompression, and therefore if any doubt exists as to the nature of the obstruction the abdomen should be opened. Internal strangulations are usually associated with early signs of shock, severe intestinal colic and early reflex vomiting. Wangensteen lays great stress on the demonstration of rebound tenderness, which is not present in the early stages of simple obstruction unless the obstructing lesion is inflammatory in origin. It must be admitted, however, that the differentiation of simple from strangulation obstruction may be very difficult, and in late cases probably impossible.

The mechanical obstruction which supervenes on a recent abdominal operation is usually simple in type and the result of intestinal matting. In such cases suction treatment may be most useful; in quite a large proportion of patients if intestinal distension is relieved, the bowel readjusts itself to the new conditions and the continuity of the intestinal tract is re-established. Should

for continuous suction; it is too liable to become blocked and requires constant attention. Once the stomach is reached, suction is commenced and continued until the stomach is empty, when the patient is turned on the right side and the tube slowly advanced until the duodenum is reached and its contents aspirated. If gastric distension is very marked it may be impossible to intube the duodenum, but it is usual to find that gastric aspiration also succeeds in withdrawing duodenal contents. Gastro-duodenal suction is continued until the abdominal distension is relieved and the aspirated material is no longer dark and foul-smelling. Throughout the treatment the patient is allowed to drink freely; this fluid is, of course, immediately re-aspirated, but the psychological effect is considerable. In a successful case the bowels move spontaneously, and not until then, or at least until flatus is passed, may a purgative be given. Intestinal decompression must be accompanied by fluid and salt replacement; sufficient saline is given to raise the plasma chloride concentration to normal and thereafter the volume of fluid removed by suction, less the amount drunk, is replaced by an equivalent amount of normal saline. This will ensure adequate salt replacement, but in addition normal water balance must be maintained, and this has been seen to require 3500 c.c. of water daily, which is given in the form of 5 per cent. glucose in distilled water.

The clinical notes of a patient who has recently been under my care may be quoted as indicating the possibilities of this method of treatment.

A woman aged 41 was brought to hospital with the history that she had received a severe blow on the abdomen forty-eight hours previously. This injury was quickly followed by severe abdominal pain and later by vomiting, which on admission to hospital was "fæcal" in type. She showed all the signs of dehydration, pulse 140 and of poor quality and temperature subnormal. The abdomen was tender, rigid and markedly distended and the presence of free fluid was demonstrated. A diagnosis of traumatic perforation of the intestine was made. A small œsophageal tube was passed and a large quantity of foul-smelling fluid removed from the stomach; 2000 c.c. of saline was given rapidly by the intravenous route, followed by 1000 c.c. of blood, administered throughout the course of the operation, which was carried out under gas and oxygen anæsthesia. The peritoneal cavity was full of intestinal contents, the result of a large jejunal perforation, and most of the small intestine was grossly

tion are poor subjects for abdominal exploration. In such cases conservative treatment is at least as likely to produce good results as is operation, in fact the lowest mortality (6 per cent.) yet recorded in a series of mechanical obstructions was achieved by conservative treatment (Rea) If suction treatment is employed in these cases frequent abdominal examination should be carried out, as the development of tenderness is an indication for replacing attempts at intestinal decompression by operation

Some difference of opinion exists as to the correct procedure to be adopted once operation has become necessary. In an early case division and removal of an obstructing band is a relatively safe procedure, but if numerous adhesions are present an ileo- or jejuno-transverse colostomy is indicated. In advanced cases an enterostomy is usually considered to be the method of choice, although I have obtained satisfactory results from an anastomosis between the transverse colon and a point high in the jejunum This method has the advantage of conserving the jejunal contents which are absorbed by the colon. I may say that only once, three years later, have I had to reopen the abdomen to undo such an anastomosis, which supports the contention that, given time, many obstructions due to adhesions tend to undergo natural relief.

Strangulation Obstruction.—This type of obstruction is met with in various forms, but when it follows upon a previous laparotomy it usually occurs as a strangulated incisional hernia, or as the result of an adhesion ensnaring a segment of bowel or giving rise to a volvulus. In such cases operation is imperative, and I quote Wangensteen · " He who elects to employ suction in the presence of intestinal colic accompanied by rebound tenderness of the abdominal wall does it at the great risk of treating a patient conservatively who has a strangulating obstruction " Aird, Holt and others have shown that, as a result of the primary venous obstruction, a considerable volume of blood may be held up in the affected segment of bowel, and there is the still more important risk of peritoneal infection as a result of gangrene of the intestine apart from the danger of the early absorption of toxins from the strangulated bowel on which they lay considerable stress While early operation is indicated, pre-operative treatment must not be omitted altogether; washing out of the stomach and the rapid infusion of blood and saline render operation safer. If the bowel is viable, simple relief of the strangulation followed by continuous suction is all that is required, but if resection of intestine is

such a fortunate result not ensue, provided water and salt balance have been maintained, no harm has been done and operation is carried out on an intestine which has been at least partially decompressed. The obvious objection to the conservative treatment of mechanical obstruction is that the nature of the lesion cannot be determined with certainty. The following clinical notes illustrate this point.

A few months ago I had occasion to undo a gastroenterostomy which had been performed elsewhere three months previously, and which had been followed by very persistent vomiting. At operation I found that the patient, a woman aged 60, had a well-marked duodenal ileus and no pyloric obstruction. The gastroenterostomy was disconnected and a duodeno-jejunostomy established. An indwelling tube and suction were employed as a precautionary measure, and, as had been expected, a considerable quantity of duodenal contents and altered blood were aspirated during the first forty-eight hours. Contrary to expectations the aspirated material continued to be considerable in amount and did not become clearer. This state of affairs continued for four days, and although the patient's general condition did not deteriorate, salt and water balance having been maintained, it became obvious that an obstructive lesion had developed. The abdomen was reopened and it was found that the portion of jejunum which had been separated from the stomach and closed had become adherent to a coil of intestine at a lower level and so caused an acute mechanical obstruction. It is important to note that at no time during this obstructive phase did the patient show any signs of abdominal distension or complain of intestinal colic. Following relief of the obstruction the patient made a rapid recovery and is now completely free of all dyspeptic symptoms. It will be readily appreciated that the freedom from symptoms following the first operation was due to early and continuous intestinal decompression, and that the patient's ability to undergo a second operation was much greater than would have been the case had she been suffering from increasing abdominal distension, intestinal colic and vomiting, over a period of days.

In this paper I am not advocating the conservative treatment of mechanical obstructions of the small bowel, but there is no doubt that considerable advances along these lines have been made. In the early case, with suitable pre-operative preparation and post-operative care as already outlined, satisfactory operative results may be expected, but patients in the late stages of obstruc-

tion are poor subjects for abdominal exploration. In such cases conservative treatment is at least as likely to produce good results as is operation, in fact the lowest mortality (6 per cent.) yet recorded in a series of mechanical obstructions was achieved by conservative treatment (Rea). If suction treatment is employed in these cases frequent abdominal examination should be carried out, as the development of tenderness is an indication for replacing attempts at intestinal decompression by operation.

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necessary the problem is very different In 1936 I published a paper advocating the more frequent use of stage resections of the small bowel, being content with exteriorisation of the affected loop as the first stage. Further experience with this procedure has not lessened my belief in its value, but it has brought to light the need for certain precautions. The first stage consists in the relief of the strangulation and the rapid delivery of the gangrenous segment, together with an inch or two of viable bowel at each end. The wound is now partially closed around the exteriorised loop, strands of iodoform wool being left in the depths of the wound round the intestine. This iodoform pack helps to seal off the peritoneal cavity, but, more important, it simplifies greatly the separation of the intestine from the abdominal wall when the time comes to reconstitute the intestinal tract. Formerly, the resection was postponed for twenty-four hours, but as a certain amount of toxic absorption persists it has been found more satisfactory to complete the resection at once, this being done after the closure of the wound. Catheters are introduced into the proximal and distal portions of bowel which project from the wound and are advanced sufficiently far to ensure that their tips lie well below the level of the abdominal wall. Failure to place the catheters well inside the bowel may result in ineffective drainage. Finally, the bowel-ends are closed and invaginated around the tubes. All the intestinal contents from the proximal portion of bowel are collected, and from time to time they are introduced into the distal bowel through the catheter. This has been found to give better results than the replacement of the intestinal secretions by intravenous saline, although a certain amount of saline and glucose are required as well. In one or two cases the result of giving the patient his own intestinal secretions has been dramatic in its effects, the general condition being improved out of all knowledge in a few hours. It has been noted that if the intestinal secretions are introduced when cold, intestinal colic is apt to occur, but this can be avoided by warming the fluid to body temperature. Attempts have been made to obtain a similar result by doing an extra-abdominal anastomosis through a tube as described by the late Sir David Wilkie, but this has not been successful ; the proximal bowel appears to be incapable of propelling its contents through the inert uniting tube. Every effort must now be made to improve the patient's condition as rapidly as possible, so that the final stage can be carried out before the enterostomy tube becomes loose and intestinal leakage leads to skin irritation or wound infection,

which is particularly liable to occur in stout patients. The wound and peritoneal cavity are freely opened and a formal resection of the bowel-ends is performed, the continuity being established by a lateral anastomosis. In a recent paper from the Mayo Clinic, exteriorisation is advocated for cases of intussusception when resection is required. From personal experience I can confirm that this stage procedure is well tolerated by children, although I have never had occasion to employ the method in a very young child.

The value of the method which I have described is illustrated by the following note: I have under treatment at the present time a woman aged 63 who was admitted to hospital forty-eight hours after the very sudden onset of acute abdominal colic which persisted and was associated with repeated vomiting. Her general condition was poor and she showed all the signs of dehydration. Abdominal examination revealed a mid-line suprapubic scar, distension especially marked low in the left iliac fossa and very striking rebound tenderness in the same region. A diagnosis of internal strangulation by a band was made, and after rapid pre-operative preparation, including gastric lavage, blood transfusion followed by saline 2000 c.c , the abdomen was opened, a section of gangrenous ileum about 18 inches in length was found to be ensnared by a single band in the pelvis. This was divided and removed and the bowel rapidly brought outside the abdomen and the wound closed as already described. The gangrenous portion was resected, catheters introduced, and when drainage commenced after about twelve hours the intestinal contents were introduced into the distal bowel. An indwelling gastric tube was employed for forty-eight hours, and saline and isotonic glucose solutions were administered intravenously until sufficient chlorides had been replaced and dehydration overcome. The final stage of resection and lateral anastomosis was carried out on the seventh day and since then the convalescence has been uneventful apart from a mild wound infection.

Much remains to be done before all the problems associated with acute intestinal obstruction are solved, but in the maintenance of fluid and salt balance and intestinal decompression by an indwelling tube, we have the means of radically reducing the mortality. Valuable as these methods are, they can only achieve real success if the patient is presented for treatment before dehydration and hypochloræmia have caused serious bodily deterioration.

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THE PROBLEM OF PERI-RECTAL SUPPURATION

By T. McW MILLAR, F.R.C.S.E.

SUPPURATIVE conditions about the rectum and anus occupy but a small part of the field of rectal surgery, but they present to the surgeon many problems in pathology, diagnosis and treatment. An intimate knowledge of the anatomy of the region is here, as elsewhere, essential for accurate diagnosis and correct treatment, and attention is therefore in the first place directed to some anatomical points of importance.

The Musculature of the Ano-Rectal Region and Anal Canal

Milligan and Morgan,[1] in their paper on the surgical anatomy of the anal canal, have done much to clarify this subject, and I feel I cannot do better than borrow freely from their clear descriptions.

The *sphincter ani externus* is a laminar muscle consisting of layers of superimposed fibres. When fully differentiated it consists of three parts—subcutaneous, superficial and deep, the two latter being sometimes blended and inseparable. The first and third parts are annular muscles without attachment to the coccyx, the second is elliptical and is attached to the coccyx

The *subcutaneous external sphincter* is easily seen and felt below the skin, and is commonly exposed in operating for hæmorrhoids. It lies in the same plane as the internal sphincter, from which it is separated by a ring of fascia derived from the longitudinal muscle of the rectum—the anal intermuscular septum. It encircles the lowest part of the anal canal

The superficial and deep portions of the *external sphincter* embrace the internal sphincter. The deep portion is in contiguity with and blends with the fibres of the pubo-rectalis part of the levator ani in the posterior half of its circumference

So far as the rectum is concerned, the *pubo-rectalis* is the only part of the levator ani of any importance. It is the best developed part and is of great importance in rectal function. Its fibres pass from their origin in the region of the symphisis pubis backwards and downwards round the lower and lateral aspects of the

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continence has been greatly exaggerated. Continence depends on the integrity of the ano-rectal ring.

The *ano-rectal ring* is a complete fibro-muscular band composed of the internal sphincter, the longitudinal muscle, the pubo-rectalis and the deep portion of the external sphincter.

The following rules with regard to division of muscles in the operative treatment of fistulæ can therefore be laid down:

(1) The subcutaneous portion of the external sphincter can be freely divided without fear of incontinence. It is unessential as far as sphincteric function is concerned. This is important, as in the majority of cases the main track of a fistula enters the anal canal in close relation to this muscle.

(2) All the anal sphincter muscles below the ano-rectal ring may be divided without harmful loss of control. The ano-rectal ring must always be left intact.

(3) Division of the sphincter muscles can always be carried out more freely posteriorly than anteriorly, because the anal canal is shorter anteriorly, the pubo-rectalis muscle not entering into the formation of the anterior part of the ano-rectal ring. This is fortunate, for most high fistulous openings are situated posteriorly.

The Origin of Peri-Rectal Infections

Infection may reach the peri-rectal and peri-anal tissues by three routes: (1) by the blood stream as a metastatic focus from some primary source in the same way as occurs in many cases of peri-renal suppuration; (2) through the medium of septic lymphangitis or septic phlebitis, from a wound or breach of the lining membrane of the rectum or anal canal or of the perineal skin, (3) by extension from a neighbouring source of infection. It may be said at once that the first method is rare, but that it does occur. Infection by the third method also occurs infrequently. The second mode of invasion is the common one and requires further consideration.

The point of entry of the infection is commonly in the lower rectum or anal canal. Occasionally there may be a definite wound in this area produced by a foreign body in the fæces or by a foreign body inserted into the rectum. A badly given injection for hæmorrhoids may be sufficient to produce the primary lesion Other conditions which occur commonly in the ano-rectal region may provide the clue to the etiology, such as

rectum, and, meeting the corresponding fibres from the opposite side, form a powerful loop or girdle which slings the ano-rectal junction to the symphisis pubis. The lower border of this muscle is intimately attached to the deep portion of the external sphincter, and is easily identified by the finger at the ano-rectal ring

The *longitudinal muscle* of the rectum becomes fibro-muscular at the upper end of the anal canal, in the posterior half of which it blends with the pubo-rectalis muscle, and in the anterior half with the deep external sphincter. It ends by dividing into two or three septa which ensheath the various portions of the external

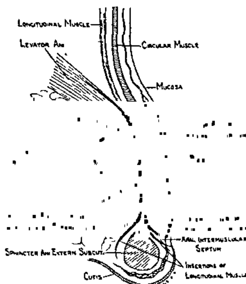


Fig. 1.—Diagram illustrating the ano-rectal musculature

sphincter. The uppermost septum, when present, passes outwards into the ischio-rectal fat between the superficial and deep portions of the external sphincter The lowest septum passes outwards below the subcutaneous external sphincter, while the third and most important one, which is the main downward continuation of the muscle, passes between the internal sphincter and the subcutaneous external sphincter to gain attachment to the skin of the anal canal in the region of the muco-cutaneous junction. It forms the *anal intermuscular septum*. I have described this arrangement in some detail because these septa act as planes along which suppuration spreads, and the main tracks and openings of fistulæ bear a definite relation to them

The *internal sphincter* is merely the thickened lower end of the circular muscle layer Its importance with regard to

have been paid to this lesion, either as a cause of anal pain or discomfort, or as a possible source of peri-anal abscess or fistula, many authorities in America believe that it is the commonest cause of inflammatory conditions about the anus. Thus Bochner [2] states that 90 per cent. of all para-anal inflammatory disease is of non-specific origin and is directly traceable to an acute cryptitis, and Synnott [3] that it is a well-known fact that the internal opening of fistula-in-ano is almost always found in an infected crypt.

The sequence of events may therefore be that the inflammatory process starts as a cryptitis and extends into the peri-anal tissues, possibly along the ducts of peri-anal glands when such exist. The infection thus passes into the anal muscles and through them into the cellular tissue of the ischio-rectal fossa, where abscess formation occurs and rupture of the abscess leads to the formation of a fistula.

Inflammation of the Peri-anal Intramuscular Glands.—There is sound evidence that there exists in the peri-anal region, at least in some individuals, glandular structures which penetrate into or through the internal sphincter muscle, and that these glands are liable to become infected. Gordon-Watson and Dodd [4] have described these glands and quote three clinical cases of ano-rectal abscess in which histological evidence of the presence of intra-muscular glandular structures was found. Lockhart Mummery [5] referred to these glands as possible pathways of infection from the lumen of the anal canal to the peri-anal muscular tissues and spaces, while Harris [6] explained the existence of these glandular structures on embryological grounds. In America, Tucker and Hellwig [7] demonstrated the presence of tubular ducts opening into the mouths of the crypts of Morgagni.

The peri-anal intramuscular glands are variable in their number and distribution but can be demonstrated by microscopic section in most rectums. They are simple tubular or branched structures usually lined by transitional epithelium or, according to some observers, by stratified squamous epithelium near the bowel end, and by two or more layers of columnar cells in their deeper part. The glands may be found in the substance of the internal sphincter and the levator ani or on the upper or lower surface of the latter. Their presence in the external sphincter has been demonstrated in operation specimens.

The ducts open into the anal canal, and according to Tucker and Hellwig actually open into the mouths of the crypts.

thrombosed and infected hæmorrhoids, anal fissure and infected sebaceous glands at the anal margin. But even when all these causes have been considered, we are still left with many cases in which the *fons et origo* of the infection is unknown, and we are driven to ask if there is not some other lesion which occurs commonly and which may lead to peri-rectal suppuration.

This question may be answered in the affirmative. At least two such pathological conditions have been described. The first is inflammation of the crypts of Morgagni, to which the term

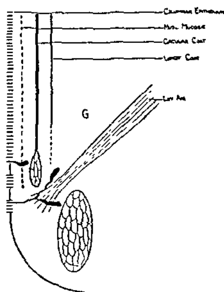


FIG 2.—Diagram showing the possible sites of peri-anal glands or ducts (after Harris)

cryptitis is applied, and the second is inflammation of the peri-anal glands.

Cryptitis.—The crypts of Morgagni are small blind pockets bounded towards the lumen of the anal canal by the semilunar anal valves, on their deep aspects by the rectal mucosa and laterally by the lower ends of the adjacent columns of Morgagni. The crypts open upwards towards the rectum. The number of crypts corresponds to the number of columns present.

It seems reasonable to suppose that not infrequently particles of fæcal matter pass into these crypts, lodge there and set up irritation and inflammation, which may spread outwards through the wall of the anal canal and give rise to some form of ano-rectal suppuration. While in this country little attention appears to

for a varying distance before actually entering the lumen. In any case it is most likely to open into the anal canal posteriorly. If it passes behind the anal canal to the opposite ischio-rectal fossa it will probably burst through the skin over both fossæ, but the opening into the bowel will again be posterior. An abscess situated in the anterior part of the fossa may and commonly does pass straight towards the anal canal and open into it in its anterior half.

The diagnosis of ischio-rectal abscess is usually straightforward. The extent, size and situation of the abscess can be accurately determined with the forefinger in the rectum and the thumb over the abscess externally—the so-called bi-digital examination.

Pelvi-rectal abscesses are rare, but serious when they occur. The pelvi-rectal space is not usually infected from the rectum at all, but from such sources as the prostate, base of the bladder and seminal vesicles in the male and from the parametrium and broad ligament in the female. If the abscess is acute it may perforate into the peritoneal cavity and give rise to general peritonitis. If less acute it eventually perforates the levator ani close to the rectum, enters the ischio-rectal fossa and then presents the features of an ischio-rectal abscess for which it may be mistaken. This abscess never perforates into the bowel.

A *para-rectal abscess*, on the other hand, always perforates into the rectum, penetrating the muscular wall of the bowel to do so. This abscess forms within the fascia propria of the rectum, and is prevented from infecting the pelvi-rectal space proper by this strong investment of fascia.

Treatment of Ano-rectal Abscesses

Only the general principles of treatment and after-treatment need be outlined :—

(1) Early incision should be carried out in all cases. There is no place for palliative treatment.

(2) Incisions must be free and may be cruciate or T-shaped, the cross of the T being made parallel to the anal canal and lateral to the outer margin of the subcutaneous sphincter, and the stalk of the T outwards from the first incision, and at right angles to it. If incisions are free, skin need not be ruthlessly sacrificed.

(3) Any septa crossing the abscess cavity should be gently broken down

(4) If an opening into the anal canal is discovered, no attempt

While it is difficult to prove that infection of these glands commonly leads to peri-rectal or peri-anal suppuration, we have in them a possible track along which infection may spread from the bowel into the peri-anal tissues and, if the glands indeed sometimes open into the crypts, a further reason for considering cryptitis as of etiological significance.

Ano-Rectal Abscesses

I do not propose to say much about the various types of abscess which form in relation to the anus and rectum. They are well recognised and differentiated, and are classified as the subcutaneous, the submucous, the ischio-rectal, the pelvi-rectal and the para-rectal.

The *subcutaneous*, *subcuticular*, or *peri-anal abscess* is usually a small superficial abscess close to the anal margin. Its diagnosis and treatment present no difficulties.

The *submucous abscess* forms as a rule in the lower rectum, usually on the lateral wall. It is an uncommon variety, and is recognised by the local and general signs of acute infection in this region. Digital examination, which may be extremely painful, reveals a somewhat elongated, smooth, tense and tender swelling occupying a portion of the rectal wall. The swelling may be seen through the proctoscope, the mucous membrane overlying the abscess being red and showing numerous dilated blood vessels.

The *ischio-rectal abscess* is the commonest and most important variety. The fatty tissue of the fossa offers little resistance to any infection which reaches it, so that suppuration occurs readily. Once pus has formed, the abscess cannot extend upwards or laterally, being limited by the levator and its fascial sheath and by the lateral wall of the pelvis. It may extend downwards towards the skin surface, medially towards the anal canal or, passing behind the anal canal it may find a weak spot in the incomplete attachment of the levator ani to the ano-coccygeal ligament and pass through this gap to reach the ischio-rectal fossa of the opposite side. If it points towards the anal canal it may pass through to the mucous membrane along one or other of the tendinous expansions of the longitudinal muscle. Thus it may enter the anal canal at the level of the anal intermuscular septum, or pass between the superficial and deep portions of the external sphincter, perforate the internal sphincter and enter at a higher level. Sometimes it will pass upwards in the submucous tissue

for a varying distance before actually entering the lumen. In any case it is most likely to open into the anal canal posteriorly. If it passes behind the anal canal to the opposite ischio-rectal fossa it will probably burst through the skin over both fossæ, but the opening into the bowel will again be posterior. An abscess situated in the anterior part of the fossa may and commonly does pass straight towards the anal canal and open into it in its anterior half.

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(3) Any septa crossing the abscess cavity should be gently broken down.

(4) If an opening into the anal canal is discovered, no attempt

should as a rule be made to lay this open at the time of the primary operation. If a fistula results it should be dealt with by operation a few weeks later.

(5) The cavity should not be packed with gauze, unless hæmorrhage is brisk. A large flat wet dressing of gauze is sufficient.

(6) In the after-treatment, tight packing should be avoided. Hot baths are taken from an early stage, and wet dressings are applied till the wound has granulated, care being taken to obtain healing from the depth to the surface.

Ano-rectal Fistulæ

The problem with regard to fistulæ lies not so much in the method of their causation or in the diagnosis, but in the treatment.

A fistula is, in the majority of cases, the contracted down cavity of an ano-rectal abscess, and is thus usually the direct result of such an abscess. It is a fibrous tissue tube or channel lined by or filled with granulations which opens on the skin of the perineum and/or into the lumen of the anus or rectum. Fistulæ which open only on to the skin or into the lumen of the bowel are actually sinuses, but by use and wont the term fistula is also applied to these with the qualifying adjectives blind internal or blind external, to indicate more accurately their nature and their course

The first object in diagnosis is to make sure that the fistula present is in fact a fistula-in-ano, and not one of several other types of fistula or sinus which open in the perineum and to which I will refer later. The second object is to establish the type of fistula present and to determine its course, its extent and the position of its openings

Methods of Examination

By inspection the position and numbers of the external openings are ascertained, while the appearance of the openings may point to a specific infection, *e g* tuberculosis The external opening may, at the time of examination, be closed and its position revealed only by a dimple of scar tissue, or it may be so small that it escapes detection. Its position may then be demonstrated by pressure over the track which causes a bead of pus to appear.

Careful palpation of the perineum will usually reveal the site and direction of the main track of the fistula and of secondary

tracks, if such are present. The latter are usually subcutaneous. Further palpation by digital examination of the rectum will usually discover the internal opening, which is felt as an indurated nodule, a fibrous dimple, or possibly a small indurated ulcer. Sometimes the internal opening can only be found by passing a probe from the external opening along the main track. The relationship of the internal opening to the ano-rectal ring is noted.

Proctoscopic examination may be necessary, especially in cases with submucous tracks when the pressure of the end of the instrument on the fistulous track may force out a little pus and so reveal the internal opening. The proctoscope may also be used *in conjunction with injection of the fistula with methylene blue* as a method of diagnosis, though such injection is more frequently used as an aid to operation, the injected track being stained throughout with the dye. This is a method advocated by some surgeons, though I personally have not made much use of it, and have not found it very helpful on the occasions on which I have used it. A 5 per cent. aqueous solution of methylene blue is suitable for use in this way, the injection being made by inserting the nozzle of the syringe into the external opening.

Injection of the track with lipiodol and subsequent X-ray examination—using either ordinary or stereoscopic films—is occasionally useful, especially in demonstrating the extent and possibly the origin of long tracks such as admit a probe for 3 to 4 inches and pass upwards parallel to the bowel.

Sigmoidoscopic examination is seldom necessary in the diagnosis of anal or rectal fistulæ, but it may be advisable in certain cases with an internal opening high in the rectum or to exclude the presence of disease at a higher level than can be reached by the proctoscope.

Classification of Ano-rectal Fistulæ

While Miles' classification of fistulæ is comprehensive, that of Milligan and Morgan, based on their anatomical researches into the anal musculature and on palpable landmarks in the anal canal, seems to me to be simpler and more helpful from the point of view of treatment. It is as follows —

(1) Subcutaneous and submucous fistulæ.

(2) Fistulæ with main tracks *entering* the anal canal *below* the ano-rectal ring (anal fistulæ)—(*a*) low level anal fistulæ and (*b*) high level anal fistulæ.

(3) Fistulæ with track *extending above* the ano-rectal ring (ano-rectal fistulæ)—(*a*) with internal opening into the rectum; (*b*) without internal opening; and (*c*) with main track opening into anal canal below the ano-rectal ring.

Principles of Surgical Treatment of Fistulæ

Surgical treatment is almost invariably necessary to promote healing of a fistula-in-ano.

There are three possible methods: (*a*) Incising the track from end to end and leaving a flat open wound to heal by second

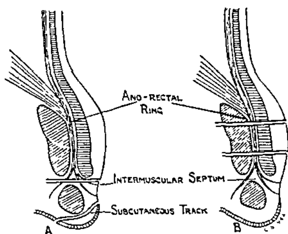


FIG. 3—(*a*) Subcutaneous and low-level anal fistulæ. (*b*) High-level anal fistulæ.

intention; (*b*) excising the fistulous track in its entirety and leaving the open wound to granulate; (*c*) excising the track and suturing the wound, the aim being to obtain healing by first intention

The most reliable and practical method of operating is the first, incision of all tissues overlying the track from the external to the internal opening and removal of sufficient skin from the edges of the incision to leave a flat, saucer-like wound. The difficulty lies in the fact that the track is usually related to the anal muscles, some of which may be in the overlying tissues and therefore require division if the track is to be fully laid open.

Time does not allow me to deal fully with the operative treatment of the various types of fistulæ as detailed in the above classification, so I will mention only a few special points

Subcutaneous fistulæ are easily dealt with as they are superficial to all the anal muscles.

Submucous fistulæ are stated to follow a circular or curved course above the ano-rectal ring. The track therefore crosses the line of the branches of the superior hæmorrhoidal vessels which, running in the submucosa, are in the roof of the track. Laying the track open into the bowel may therefore lead to hæmorrhage which may be difficult to arrest. The method of destroying the mucosal roof with strangulating ligatures is therefore advised.

Anal Fistulæ—Low Level.—The majority of fistulæ-in-ano fall into this group. The main track passes towards the anal wall along the line of the anal intermuscular septum, *i.e.* deep to the subcutaneous sphincter, while from this level a submucous extension may run upwards for some distance. The main track may be laid open to the surface, the subcutaneous sphincter being cut across in doing so, without any fear of incontinence. The submucous extension, if present, is treated as a submucous fistula.

Anal Fistulæ—High Level.—This type is fortunately less common, for it presents a more difficult problem. It includes those fistulæ of long standing of the single or double horse-shoe type. The internal opening is usually posterior and higher in the anal canal, though still below the all-important ano-rectal ring, and the surgeon must be sure that his incision through the musculature posteriorly will not divide the ring. If he can be sure on this point, the whole track may be laid open at one operation. If any doubt exists the track into the anal canal should be left to be dealt with at a later operation—the two-stage method. A silk thread may be passed through the track and tied loosely round the muscle to enable the surgeon to find it easily at the second operation. Alternatively, the silk thread may be tied tightly so that it gradually cuts through the muscle. The idea underlying both methods is that the exposed muscle will become to some extent fixed by scar tissue, so that, when it is divided, less retraction will occur. The soundness of this idea is doubted by some, who would argue that the preservation of continence is due not to the two-stage method of operation, but rather to the preservation of the ano-rectal ring which has not been divided in the second stage. However this may be, it would appear to be sound practice to operate in two stages when the internal opening is high in the anal canal and there is any doubt about its relation to the ano-rectal ring.

Ano-rectal Fistulæ—All types of fistulæ in this group are

rare. The first, with an internal opening into the rectum, may be the result of a para-rectal abscess, the second of a pelvi-rectal abscess, while the third is really an anal fistula with a secondary sinus passing up high into the ischio-rectal fossa. In all of these types, opening the complete track into the bowel would divide the ano-rectal ring and lead to incontinence. The principles of treatment are the same for all types—free incision of the track outwards towards the ischial tuberosity, or, preferably backwards to the level of the coccyx, as advised by Milligan and Morgan, and free excision of the skin over the ischio-rectal fossa. The internal opening in the third type is dealt with at a second

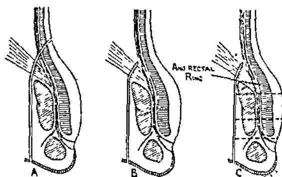


FIG. 4—Diagram showing three types of ano-rectal fistulæ.

operation carried out when the deep portion of the wound has become filled with granulation tissue to below the level of the ano-rectal ring.

Sinuses and Fistulæ not originating in the Anus and Rectum

There are a number of conditions which give rise to the formation of chronic sinuses and fistulæ which have no etiological or anatomical connection with the bowel. Some of these may be mistaken for anal or rectal fistulæ, and it is therefore necessary to make some reference to them

Fistulæ opening in the anterior part of the perineum may be of *urethral* origin. They commonly arise from the bulbous portion of the urethra either as a result of trauma or of urethral infection. Very commonly the urethral perforation has occurred behind a stricture. The external openings of such fistulæ are generally to one or other side of the mid-line and in front of the transverse anal line. As the secondary track of a fistula-in-ano

may extend forwards and open over the anterior perineum, a mistake in diagnosis may occur. The distinction, however, should be readily made. Urine commonly escapes from a urethral fistula, never from a fistula-in-ano. Induration in the ischio-rectal fossa, as distinct from the subcutaneous tissue, is always present in an ano-rectal fistula and never in a urethral one, and the internal opening of an ano-rectal fistula is usually palpable.

The fistula—or more correctly the sinus—resulting from a *pelvi-rectal abscess* which has burst through the levator ani into the ischio-rectal fossa and then through the skin, may readily be mistaken for an ischio-rectal fistula. While such a pelvi-rectal fistula is rare, it is well to bear the possibility in mind, as the method of dealing with it is entirely different from that used in a fistula-in-ano.

A *pre-sacral fistula* is again a sinus—not a true fistula. It may originate as a pre-sacral abscess, the result of infection, occasionally of a tuberculous nature, of the pre-sacral lymph nodes. The pus which forms in the pre-sacral space lies between the sacrum and the fascia propria of the rectum and, gravitating downwards, passes between the levator ani and the coccygeus to burst through the skin about an inch on either side of the coccyx. The site of the opening and the fact that a probe introduced into the external opening passes upwards for several inches parallel to the bowel, should suggest the nature of the condition. The extent and direction of the track can be confirmed by lipiodol injection.

A *pilonidal sinus* may occasionally cause difficulty in diagnosis. As a rule the pilonidal sinus is easily recognised by its position close to the upper end of the natal cleft, and by the presence of one or more minute congenital openings in the upper end of the cleft itself. I have, however, operated on a case in which a secondary track from a pilonidal sinus passed forward in the perineum and opened on the surface a little to one side of the anus and in front of the transverse anal line. In a recent case methylene blue, injected into what was thought to be the opening of a fistula-in-ano, escaped from the opening of a pilonidal sinus. Such cases point to the necessity for careful examination before undertaking any surgical operation for the cure of such fistulæ or sinuses.

Finally reference might be made to recto-urethral, recto-vesical and recto-vaginal fistulæ. Suppuration may be the cause of any of these, and while a prostatic abscess due to gonorrhœa

is the commonest cause of a recto-urethral fistula, the latter two are usually due to trauma or malignant disease.

Tuberculous Fistulæ-in-Ano

This somewhat sketchy account of ano-rectal fistulæ would be incomplete without some reference to tuberculous fistulæ. Probably some 10-15 per cent. of all fistulæ-in-ano, in this country



FIG 5.—X-ray afte... sinus. The ... successfully

at least, are tuberculous. Most of them occur in subjects suffering from active pulmonary tuberculosis, and the recognition of the tuberculous nature of a fistula sometimes leads to the diagnosis of the lung disease The tuberculous fistula may develop insidiously or may be the sequel of a typical acute peri-anal or ischio-rectal abscess The condition may be recognised ... the chara... and ordi... ...logical examination of tissue removed at operation will discover most cases of tuberculous infection, and is incidentally a precaution which should never be omitted in operating on fistulæ

In the presence of active pulmonary disease no attempt at radical cure should be made, operation being undertaken solely to provide adequate drainage Gabriel, who divides tuberculous fistulæ into superficial and deep varieties, states that the superficial variety is a localised lesion, usually anterior to the anus, with extensive undermining of the skin. He recommends complete excision of the undermined skin and cauterisation of the whole wound with the flat diathermy electrode and claims excellent results from this method of treatment. The deep variety is very often inoperable.

Peri-rectal Suppuration in other Diseases of the Colon and Rectum

A recent case, thought at first to be a simple ischio-rectal abscess, but later proved to be a case of proctitis or early ulcerative colitis, points to the necessity for keeping such a possibility in mind. Rankin and Graham state that there is strong reason to believe that chronic ulcerative colitis almost invariably begins in the rectum, and Buie records that in over 1000 cases of this disease there was no instance in which the rectum was not involved. In 48 cases of ulcerative colitis, Spriggs [8] found 14 with local rectal disorders, 8 of these suffering from fistula, abscess or fissure. Involvement of the rectum would thus appear to be an invariable feature of this disease, and peri-rectal suppuration at least an occasional accompaniment, and possibly an early sign.

Again a recent case of regional ileitis developed an ischio-rectal abscess and fistula—not a surprising development in view of the diarrhœa which was present. What is of interest, however, is to find that Penner and Crohn [9] state that it is remarkable how frequently simple fistula-in-ano was the first clinical manifestation in a series of 50 cases of ileitis, an indication of how careful investigation of a case with an apparently local peri-anal condition may reveal the presence of more serious disease of the intestine. The same authors report three cases of regional ileitis who developed peri-anal sinuses in the course of the disease, and submit evidence in support of their belief that these sinuses were due to direct fistulisation from the diseased ileum to the rectum or peri-rectal space and so to the perineum They conclude that every case of fistula-in-ano deserves careful clinical pre-operative study, including, when necessary, proctoscopy and X-ray examination of the chest and of the intestinal tract.

In conclusion, I would like to make two points regarding the treatment of peri-rectal suppuration—one a cautionary note, the other a plea for a somewhat radical procedure. The first is, to use the words of Miles, "that it may be better to endure the discomfort of a discharging sinus rather than run the risk of permanent loss of control." The second is that, in the occasional severe case, the beneficial effects of a temporary colostomy, preferably of the defunctioning type, should not be forgotten.

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UROGENITAL TUBERCULOSIS

By DAVID BAND, F.R.C.S ED

Introduction

"MANY medical problems must be left for a decision until the end of the War, either the material facts are not now available, or they must be used in the light of post-war conditions which we can hardly even guess at. But tuberculosis is an exception. The early detection of the disease is one of the most formidable problems confronting doctors; treatment cannot be instituted in good time for the great majority of cases because the lesions are relatively advanced when they are first detected, and if we could detect all cases there would be a lamentable shortage of beds for their treatment, assuming they would enter institutions at all."

This quotation from a leading article[1] in the medical press is a fitting comment on the vital statistics of the second year of the War recently analysed by Stocks,[2] which show a 10 per cent. increase in deaths due to respiratory tuberculosis, and a 17 per cent. increase in deaths due to non-respiratory tuberculosis among the population of England and Wales. In Scotland the death-rate from tuberculosis of 68 per 100,000 in 1939, has risen to 80 in 1940.[3]

In the last twenty years the campaign against tuberculosis has undoubtedly co-ordinated the respective outlooks of physician, surgeon and tuberculosis officer so that each now subscribes to the principles of rest for the treatment, and improved conditions of nutrition and environment for the eradication of tuberculosis.

Tuberculosis is a generalised infection with focal manifestations. During its invasive stage the attack is lymphogenous, and the implantations of tubercle bacilli may be air-borne or ingested. If infection is successful a stage of visceral spread is reached, because lymphadenoid resistance has been overcome, and "the lymphatic system, by its centripetal flow, empties into the blood stream all organisms which reach the great lymphatic trunks."[4] Thereafter implantations of tubercle bacilli are

Read 5th March 1942

infiltrated to bones, joints and viscera by means of the blood stream. In both stages the nature of the lesions produced in the tissues by the tubercle bacillus depends on (1) the number and virulence of the organisms, and (2) the resistance of the host. Successful implantation of tubercle bacilli to the tissues of the patient leads to focal tuberculosis. The lesions may be minimal, sparse or myriad, active or relatively quiescent. Subsequently re-infection, or a depressed general resistance lead to reactivation of such lesions even though a considerable number of years may have intervened. During 1930-35, Munro and I investigated the problem of urogenital tuberculosis from the view points of pathogenesis, treatment, and late results. For the purpose of that investigation 174 cases of extra-urogenital tuberculosis were examined for tubercle bacilluria, and 31 cases of clinically recognised renal tuberculosis were followed up in order to determine the results of treatment after a number of years had elapsed.[5] For this lecture I have taken the results of an investigation into tubercle bacilluria carried out with Munro at Glenlomond Sanatorium on an extended series of 300 cases of extra-urogenital tuberculosis, and in addition, I have included a survey of a second series of 41 cases of clinically recognised urogenital tuberculosis which I have studied during the past seven years, and whose progress I have been able to follow.

Tubercle Bacilluria

Tubercle bacilluria was formerly, and incorrectly, defined as "the passage of tubercle bacilli (in a tuberculous subject) through (1) a perfectly healthy kidney, (2) a kidney damaged in any way, but not tuberculous, and (3) a kidney changed by so-called tuberculous nephritis."[6] There was abundant evidence that bacilluria, in the absence of clinical signs or symptoms of urinary tuberculosis, did exist (see Table I). Histological confirmation of the presence of tuberculous lesions in the kidneys of subjects of bacilluria was not constant. Thus Foulerton and Hillier,[7] Jousset,[8] Rolly,[9] Kielluthner,[10] Noyes[11] and Deist[12] failed to find evidence of tuberculous disease in kidneys removed at operation or autopsy from patients who had exhibited tubercle bacilluria. Medlar[13] had shown, however, that by the method of serial sections bilateral tuberculous lesions of a microscopic nature could be demonstrated in the kidneys of patients dying

from extra-urogenital tuberculosis, and Coulaud [14] from inoculation experiments provided proof of the relationship of tubercle bacilluria to actual lesions in the renal cortex and medulla.

TABLE I

Reported Figures for Tubercle Bacilluria

Author	Total Cases	Bacilluria.	Per cent	Extra-urinary Lesion
Harris	110	25	22 7	Bone and joints
"	49	4	8 8	Pulmonary
Brown	104	..	10·0	"
Hobbs	100	..	6·0	"
Dimtza and Schaffhauser	183	8	4 3	Extra-renal
Deist	31	12	38 7	Pulmonary
Kilteuthner	19	3	15 7	"
Lotz	13	3	23 0	"
Miller	36	12	33 3	"
Mack	20	15	75 0	Extra-renal
Band and Munro	174	25	14·4	Pulmonary
Present series	300	64	21 3	"

In a previous investigation [5] Munro and I found that in a series of 174 cases of extra-urogenital tuberculosis 14·4 per cent. suffered from tubercle bacilluria. It was then noted that the tubercle bacilluria often disappeared as the patient returned to good health, and that it had been but a temporary feature of the disease. On the other hand, when death took place as a result of extra-urogenital tuberculosis, tubercle bacilluria having been present during life, bilateral cortical tubercles could be demonstrated always in serial sections made from the kidneys removed at post-mortem examination. In our final series of

TABLE II

Tubercle Bacilluria. Incidence in Sexes

		Urine T B. Positive	Per cent
Males examined	158	20	12·6
Females examined	142	44	30 9
Total	300	64	21 3

300 cases of extra-urogenital tuberculosis investigated, we have found tubercle bacilluria to occur in 21·3 per cent. (see Table II). The recovery rate was 23·4 per cent., and in those cases there has

been no recurrence of tubercle bacilluria (see Table III). This has been associated with a complete and lasting recovery from

TABLE III

Tubercle Bacilluria—64 Cases Follow-up. Recovery Rate in Five Years

Cases		Recovery.	Per cent.
Males	20	5	25·0
Females	44	10	22·7
Total	64	15	23·4

the original extra-urogenital tuberculosis which brought the patient under observation (see Table IV).

TABLE IV

Tubercle Bacilluria—64 Cases. Follow-up Table—Five Years

Males 20		
Well	Bacilluria absent	3
Improving	" "	2
Losing.	Renal condition doubtful	2
Died	Renal tuberculosis	1
Died.	No renal symptoms	12
Females 44		
Well	Bacilluria absent	6
Improving.	" "	4
Losing	Renal condition doubtful	9
Died.	Renal tuberculosis	2
Died.	No renal symptoms	23

The mortality rate in extra-urogenital cases of tuberculosis which suffered from tubercle bacilluria was high—59 per cent. (see Table V). In 27 cases the kidneys were obtained at post-mortem examination and mounted as serial whole sections.

TABLE V

Tubercle Bacilluria—64 Cases Follow-up Mortality Rate in Five Years

Cases		Deaths.	Per cent
Males	20	13	65 0
Females	44	25	56·8
Total	64	38	59 0

One thousand to 1500 serial sections were cut from each half kidney, and every fiftieth section was stained and mounted.

Such a technique provided a fairly complete histological scrutiny of the kidney. In 24 of the 27 cases bilateral cortical foci of tuberculous disease were found. The lesions were present in all stages from the epithelioid and mononuclear tubercle to the larger follicle with caseation and giant-cell formation. In many the distribution of scarring from fibrous tissue showed that healing had occurred at the site of former tubercle follicles. In a further three cases, where death occurred as a result of extra-urogenital tuberculosis in which no tubercle bacilluria had been demonstrated, the kidneys were similarly examined by serial section. No tuberculous follicles were detected in serial sections of the kidneys (see Table VI). Thus there was overwhelming evidence that the presence of tubercle bacilli in uncontaminated urine

TABLE VI

Histological Investigation by Serial Sections of both Kidneys from Patients who Died from Extra-urogenital Tuberculosis

	T B Renal Lesions Positive	T.B. Renal Lesions Negative.	Total.
T.B. bacilluria positive .	24	3	27
T B bacilluria negative .	0	3	3

The T.B lesions when found were always bilateral.

indicated a tuberculous lesion of the urinary tract, and excretion of tubercle bacilli through an uninfected kidney did not occur. Dukes [15] has drawn attention to the constant nature of the pyuria and obvious bacilluria where there is an open renal tuberculosis. In the sub-clinical type the bacilli are scanty and intermittent, but in our experience a few pus cells have been found present always in urine from which tubercle bacilli have been isolated.

Comment

The maintenance of a recovery rate of nearly 25 per cent. has been shown in the extended series, and the follow-up has been continued for several years The mortality rate of nearly 60 per cent. shows that a bacilluria in sanatorium cases is frequently a terminal phenomenon. The number of cases which develop a frank renal tuberculosis is small (under 5 per cent.). The kidneys obtained at autopsy showed no naked-eye evidence of renal tuberculosis. It was a general rule to find a scattered group of microscopic

tuberculous follicles through a neighbouring series of whole sections, and the diagnosis was unmistakable. It is quite possible to miss the infected part of a kidney if a group of whole sections should be lost in preparation, for example, in trimming the microtome. The earliest tuberculous lesions in the kidney are cortical, in relation to the glomeruli, and bilateral. The infection is blood-borne. Their only clinical manifestation is bacilluria and they are not associated with the clinical syndrome and cystoscopic or pyelographic appearances of renal tuberculosis. It is presumptive in tuberculosis that visceral spread by the blood stream may be followed, clinically, by a quiescent period of variable duration. Certain possibilities arise: (1) miliary bilateral implantations to the kidneys, part of a general and terminal dissemination; (2) scattered bilateral implantations which may heal; (3) sparsely distributed implantations which may give rise to tuberculous follicles of minute size

These minor sub-clinical lesions may *(a)* extend and coalesce, caseate and discharge tubercle bacilli from the cortical tubules to the papilla in the medulla, where ulceration and cavitation lead to infection of the calyx and renal pelvis. Thence the infection passes by intra-luminar spread to the bladder, and the clinical syndrome of ulcero-cavernous renal tuberculosis follows; *(b)* remain localised, and encysted, yet potentially active should favourable general or local conditions permit. It is from these quiescent or closed lesions that many of the chronic forms of renal tuberculosis originate. The problem of reactivation is one that concerns all focal manifestations of the general disease — tuberculosis.

Urinary and Genital Tuberculosis

Introduction. — In focal tuberculosis, where blood spread has already taken place, it is customary to regard the lungs as viscera exposed to the earliest and most numerous implantations of the bacilli. In the investigation of all tuberculous lesions it is essential to examine each system, whether clinical signs have developed within it or not, and in my earlier series of 31 cases of urinary tuberculosis I could find evidence of extra-urinary lesions in only 64 per cent. I had observed, however, that of the 16 males in the series, genital lesions were present in 7 (43·8 per cent.) and subsequently, every case of genital tuberculosis has been subjected to a complete urological study. In a second series of

39 cases of urogenital tuberculosis in the male (Table VII) there were combined lesions in the genital and urinary systems in 20,

TABLE VII

Urogenital Tuberculosis—39 Male Cases

		Per cent.
Urinary only	11	28·2
Genital only	8	20 5
Urogenital combined	20	51·3
	39	100 0

an incidence of 51·3 per cent. Wells [16], Jacobs [17] and Hinman [18] have reported on the frequent coincidence of renal and genital lesions; Menville and Priestley [19] found coincident renal lesions in 51·6 per cent. of a series of 62 cases of male genital tuberculosis studied at autopsy.

Urinary Tuberculosis

Tuberculosis in the urinary tract develops primarily in the kidney as a minute cortical lesion in relation to a glomerulus The study of autopsy specimens by the method of serial sections has demonstrated the bilateral nature of blood-borne implantations of the tubercle bacillus in cases with terminal dissemination. Thus in the clinical investigation of urinary tuberculosis the possibility of bilateral renal infection has to be borne in mind. Jacobs [17] has reported that bilateral renal lesions were present in 16 of his series of 43 cases, and in Lett's 208 cases one-third were inoperable.[20] The proportion of cases with bilateral infection varies with the source from which the patients have been selected. There is a higher proportion with bilateral renal disease to be found amongst patients who have attended a tuberculosis dispensary than amongst those who have come direct to the out-patient department of a general hospital The incidence of bilateral infection in kidneys or lungs is comparable in cases drawn respectively from dispensary or general hospital practice. Clinicians generally admit the conception of the bilateral nature of tuberculous renal lesions at the initial stage of visceral dissemination of the tubercle bacillus; but it is believed that provided the implantations are sparsely scattered, healing or encystment may be expected in one kidney, and ulcero-cavernous lesions will be limited to the other. One feature of the

investigation of tubercle bacilluria in sanatorium patients was the remarkably low incidence of clinical renal tuberculosis (see Table IV). There was the complete recovery rate of nearly 25 per cent., and the high mortality rate of nearly 60 per cent. Ulcero-cavernous renal tuberculosis is a focal manifestation of a chronic and slowly developing type, in which the progress of the lesion is determined by the dosage of tubercle bacilli implanted and the general resistance of the patient. Thus extirpation of the kidney in a properly selected case is a treatment of choice which yields an excellent recovery rate. The factors which militate against a uniformly excellent recovery rate following nephrectomy in renal tuberculosis are (1) tuberculosis of the urinary bladder and (2) the presence of extra-urinary lesions.

Comment

(1) Tuberculosis of the urinary bladder is always secondary to renal tuberculosis. The moment a renal focus becomes open, and discharges tubercle bacilli to the renal pelvis, the infection passes with the urine to the bladder. On cystoscopic examination a zone of congestion including minute tubercles can be seen in the neighbourhood of the ureteral orifice of the affected side. The subsequent progress is that of continued ulceration, fibrosis, and contracture of the bladder wall, until the final picture of the contracted bladder, distorted (golf hole) ureteral orifice on the affected side, and incompetent ureteral orifice of the opposite side has become established. For successful treatment in renal tuberculosis a diagnosis must be made long before the bladder wall has undergone widespread ulceration and contracture. Frequency and pyuria (often unsuspected by the patient) require a complete urological examination.

(*a*) Preliminary X-ray examination is often helpful, as a chronic renal focus may undergo calcification, which, though sometimes massive, usually has a localised and petechial distribution without the more homogeneous density of renal stone.

(*b*) The presence of pus cells without organisms in an acid urine has for long been the recognised clue to a diagnosis of urinary tuberculosis. A solitary bacteriological examination of the urine is negligent. Alcorn and Buchtel [21] have found that in 44·7 per cent. of samples of urine, submitted from cases of urinary tuberculosis, a secondary infection had developed. Dukes [15] has recommended the early morning specimen, and a large twenty-four

hour sample of urine as those most suitable for submission to the bacteriologist. Tubercle bacilli should be demonstrable in films made of the centrifuged deposit from adequate specimens of urine. Cultural and inoculation methods are necessary when difficulties in diagnosis occur, or when the type of organism is being investigated (see Table VIII).

TABLE VIII

Types of Tubercle Bacillus in Bacilluria

Human.	Bovine.	Total.	Bovine Per cent.
59	5	64	7 8

(*c*) Intravenous urography can usually be relied upon to provide an adequate and diagnostic pyelogram of the tuberculous kidney. Difficulties may be encountered, however, when, for the purpose of operability, an accurate estimate is required as to the health of the opposite kidney. Urologists in general are in agreement with Emmett and Braasch,[22] who insist on the necessity for catheterisation of the ureters and retrograde pyelography, if not for the recognition of the tuberculous kidney, then, very definitely, in order to obtain reliable information as to the state of its neighbour.

(2) The presence and state of activity of extra-urinary lesions require for their detection and assessment thorough clinical and radiological examinations. Intermittent febrile disturbance and, in particular, the response to rest in bed cannot be ascertained until the patient has been brought into hospital. A few weeks of observation, under sanatorium conditions of rest and hygiene, may yield an expectation of quiescence in extra-urinary lesions which permits of a future nephrectomy, with recovery and ultimate rehabilitation of the patient. Sanatorium standards of rest and therapy are the only safeguards against reactivation of extra-urinary foci when surgical interference is contemplated.

Genital Tuberculosis in the Male

In the series (see Table VII) 20 per cent. of male urogenital cases suffered from a lesion which clinically was limited to the genital tract, and few, if any, of those cases would have been recognised had there been no involvement of the epididymis. Thus in order of frequency clinical genital tuberculosis may be recognised (1) in the epididymis (100 per cent. cases), (2) in the

seminal vesicles (75 per cent. cases), and (3) in the prostate (17·8 per cent. cases) (see Table IX). Yet bilateral vesiculitis

TABLE IX

Male Genital Tuberculosis. Distribution of Lesions—28 Cases

		Per cent
Epididymo-orchitis		
Unilateral	28	100
Bilateral	7	25
Seminal vesiculitis.		
Unilateral	21	75
Bilateral	14	50
Prostatitis	5	17·8

was present in 50 per cent. of cases. These figures are at variance with those reported from the post-mortem room. Moore [23] made an autopsy study of the genital tract in 20 cases of tuberculous prostatitis, and found vesicular lesions in only 15 per cent. He believed that in tuberculous disease of the prostate the lesions were blood-borne because they were distributed in the peripheral zones of the prostate, whereas a urethral spread by contiguity produced lesions close to the lumen of the prostatic urethra. Menville and Priestley [19] found renal and prostatic tuberculosis closely associated in an autopsy study of 62 cases of genital tuberculosis. At the same time they noted that the epididymis was frequently involved while the prostate remained normal. Hammond [24] stresses the difficulties in attempting to assess the pathogenesis and mode of spread in genital tuberculosis It should not be forgotten, however, that the testis and epididymis have a generous blood supply through the spermatic artery and the artery to the vas deferens, the one from the aorta and the other from the internal iliac through its inferior vesical branch. Similarly, the prostate, seminal vesicles, and ampulla of the vas deferens are all supplied by the inferior vesical and middle rectal branches of the internal iliac artery The close relationship of these structures to one another in the median line in front of the rectum, and the intercommunications in the lymphatic drainage, as well as the intra-luminar connections through the ducts provide alternative routes for the spread of infection in the genital tract, once a tuberculous focus has become established and activated. Thus tuberculosis may be primary (1) in the prostate, as a peripheral lesion, or (2) in the urethra and ascend via the

ejaculatory duct to the vesicles, or by way of the vas to the epididymis, or (3) in the epididymis, and descend via the vas to the vesicles and by the ejaculatory ducts to the urethra

From a patient of fifty-seven years who had undergone nephrectomy for tuberculosis I had occasion, within a few months, to remove a median bar transurethrally. The specimen of tissue removed from the prostate and the urethra showed no evidence of tuberculosis, though the kidney was the seat of advanced ulcero-cavernous lesions.

Comment

Coincidence of renal and genital lesions is relatively common in urogenital tuberculosis. Although infection may spread within the genital system, or within the urinary system via the lumina of their ducts, *i.e.* by direct extension, the co-existence of the disease in the two systems may not be due entirely to direct extension from one to the other, as is sometimes stated. Coincidence of renal and genital lesions should be regarded as possible evidence of independent yet co-existing focal manifestations of the disease The abundant arterial supply to the genital tract, the frequency of genital tuberculosis in the young adult, and the anatomical distribution of the lesions favour blood-borne implantations. The absence of beading in the ductus deferens except in advanced and chronic types, the direction of the current within the lumen of the vas (which is aided by its ciliated epithelial lining), and the distribution of the lesions themselves point to a descending infection from epididymis to vesicle and thence to prostate as a ready mode of spread of tuberculosis within the genital tract

I have drawn attention to the 51·3 per cent. combined incidence of urinary and genital tuberculosis in the series under review. The need has been stressed both for a thorough investigation of extra-urinary manifestations of tuberculosis, and of the extent of the lesions within the urinary organs. The diagnostic methods available for the examination of the genital tract are numerous and accurate The external genitalia may be examined by inspection, palpation and transillumination. Granulations from discharging sinuses may be examined histologically and bacteriologically. The rectal examination should be conducted in the knee-elbow position with the full co-operation of the patient in order that the prostate, seminal vesicle, and vas deferens may be

palpated on each side. The cysto-urethroscope is available for the inspection of the posterior urethra, and a posterior urethroscopy should be included when the cystoscopic examination is carried out. Such an examination, however, should not be persisted with when inflation of the urethra is required, or if the manipulations are difficult for any reason. This is particularly important when the examination is carried out under low spinal anæsthesia, as the danger of a reflux of infected debris to ureter or ejaculatory duct may not be appreciated in the absence of pain. Massage of the vesicle or prostate is to be deprecated. The firm pressure necessary to express an adequate amount of secretion for examination in doubtful cases may reactivate tuberculous foci and precipitate a local and, rarely, a general dissemination.

The Treatment of Urinary Tuberculosis

I have laid emphasis on the need for complete rest in bed while the patient with symptoms suggestive of urogenital tuberculosis is under observation for investigation. Indeed, when extra-urogenital lesions are present it is essential to have the fullest co-operation between physician and surgeon; whether the patient should be in a general hospital or in a sanatorium at this stage is a matter for mutual arrangement. Even in cases where multiplicity of active foci of infection render ultimate surgical intervention problematical, opportunities should be sought for reconsideration of individual cases after an initial period under sanatorium care. Urogenital tuberculosis alone is so slowly progressive that a preliminary course of treatment of two or three months' duration may determine (1) the practicability of operative interference, (2) satisfactory immediate post-operative progress, and (3) the ultimate and successful rehabilitation of the patient after a prolonged convalescence.

There is only one curative therapy for urinary tuberculosis, and that is nephrectomy, in conjunction with the sanatorium life for six months or a year. It is only by surgical removal of the tuberculous kidney that cessation of the continued re-infection of the bladder can be brought about When the ureter is involved it must be removed as well. Then, and then only, may the bladder, which is never at rest, be given an opportunity to heal. Post-operative sanatorium care should be continued till residual ulceration of the bladder has been controlled, frequency of micturition restored to within normal limits, and the urine

rendered free from tubercle bacilli. The operation deaths from nephrectomy in renal tuberculosis are negligible, if the cases are properly selected and the operation conducted with gentleness. The recovery rate is good as regards the immediate prospects but, as the follow-up continues over a number of years, recurrence of bladder ulceration, reactivation of extra-urinary foci, or persistent contracture of the bladder and consequent backward pressure on the remaining kidney take their toll (see Table X). When a

TABLE X

Renal Tuberculosis Five Year General Follow-up 41 Cases

		Per cent	Females	Per cent	Males	Per cent.
Recovery—						
Complete	15	36 5	4	40	11	35 5
Residual disability	16	39 0	3	30	13	41·9
	31	75 5	7	70	24	77 4
Deaths	10	24 5	3	30	7	22·6
	41	100	10	100	31	100

Bilateral renal tuberculosis 12 per cent

complete recovery is taken to mean the complete rehabilitation of the patient to a full and active life as a wage-earner, I find that the recovery rate of 86·4 per cent. may be reduced to about 50 per cent., the ultimate mortality rate is 13·6 per cent. (see Table XI). When nephrectomy is contra-indicated the mortality

TABLE XI

Urogenital Tuberculosis 41 Cases

Results of Nephrectomy—30 Cases 73 per cent

		Per cent
Recovery	26	86·4
Deaths	4	13 6

Cause of Death.

1. Progressive hydronephrosis from contracted bladder. Uræmia following transplantation of ureter
2. Progressive hydronephrosis from contracted bladder Uræmia
3. Multiple visceral lesions, including lungs and bones Miliary spread
4. Tuberculosis remaining kidney

rate at the end of five years rises to 54 per cent, and, though a marked amelioration of symptoms may occur under sanatorium

conditions, in 30 to 40 per cent. of cases there is never more than semi-invalidism (see Table XII).

TABLE XII

Urogenital Tuberculosis. 41 *Cases*

Results when Nephrectomy contra-indicated. 11 *Cases*

		Per cent.
Deaths	6	54·5
I.S.Q. or improved	5	45·5

Renal calcification in 4 under sanatorium conditions.

Table X shows the frequency with which a slight residual disability may detract from a complete and lasting recovery. Lett[20] has found that, in London, complete recovery may be expected in 55 to 60 per cent. of cases of urinary tuberculosis, while Marion,[25] in Paris, declared his figures for complete recovery as 50 per cent. for the poorer patients and 80 per cent. for those living under better conditions. In a valuable follow-up series, de Illyes[26] found that, after fifteen years, of 119 nephrectomies for tuberculosis living in good circumstances, 68 per cent. were able to work, whereas of 322 cases living in unfavourable circumstances only 25 per cent. were able to earn a livelihood. In two of my nephrectomy cases the fatal issue was brought about from progressive backward pressure on the remaining kidney as a result of persistent cystitis with ulceration and contracture of the bladder (see Table XI). The mortality from transplantation of the dilated ureter to the bowel in such cases is prohibitive, on account of the constancy of ascending infection, and fatal pyelonephritis Wade,[27] in his extensive experience of the scope of transplantation of the ureter to the bowel, found that mortality was greatest when transplantation was carried out for carcinoma of the bladder, and when the sole remaining ureter was transplanted on account of backward pressure from the contracted bladder in tuberculosis. Keyes[28] has reported 6 cases of successful cutaneous ureterostomy without mortality Two of his patients lived useful lives for as long as nineteen years after this operation. d'Escrivain[29] has made a similar recommendation when nephrectomy has proved insufficient, and tuberculous cystitis and severe frequency have threatened the remaining kidney. In such circumstances deviation of the urinary stream supplies the essential therapeutic agent of rest in the treatment of intractable tuberculosis of the bladder. Professor J. R. Learmonth has

recently demonstrated to me a cutaneous ureterostomy he had made for a patient with intractable cystitis following nephrectomy for tuberculosis. With the co-operation of A. B. Wallace he had most effectively overcome the difficulty of fitting an efficient ureterostomy belt, by converting the projected end of the divided ureter to a nipple or teat by means of skin grafts With such a technique, and by rendering the ureterostomy belt water-tight and efficient, there is undoubtedly available for those unfortunate patients with intractable tuberculous cystitis a method of relief which will enable them not only to resume normal social intercourse, but to remain in good health for many years.

The value of a controlled sanatorium regimen in the treatment of urinary tuberculosis can never be over-emphasised. The system of complete rest in bed, followed by graded exercise, is one which has proved of the utmost value in the control of focal tuberculosis. The post-operative care on these lines should be continued for at least six months, so that the patient has been trained to seek for himself as much light and fresh air as can be made available for him in his future life. Even in the inoperable cases the progress of caseo-cavernous renal tuberculosis can be influenced in the sanatorium. By an improved local and general resistance to the disease process, fibrosis and calcification in the kidney and ureter may limit the discharge of tubercle bacilli to the bladder and lead to a relative quiescence I have noted renal calcification under those circumstances in 4 cases in the present series (see Table XII), in which 11 were inoperable. Tuberculin is probably of very real value when focal manifestations are limited and under control. The dosage should be graduated with care, and local and general reactions avoided The patients themselves rarely lapse in their attendance as out-patients when tuberculin injections are being administered, and on this account, if for no other reason, they thereby benefit.

Treatment of Genital Tuberculosis

In the localised genital lesion surgical interference should never be undertaken until the surgeon has allowed for an adequate period for rest and observation. Orchidectomy is an operation to be deplored, particularly when carried out as a routine measure The response of the patient as a whole to rest may be reflected in a marked improvement in the progress of genital foci. The employment of a suspensory belt or bandage is advantageous,

The frequency of accompanying vesicular tuberculous lesions when there are foci in the epididymis, the tendency to bilateral seminal vesiculitis, and the occurrence of bilateral tuberculous epididymitis are well known in clinical and pathological experience Bilateral epididymo-orchidectomy, with all its repercussive effects on the young adult can be avoided more frequently if conservation is made the first treatment of choice in genital tuberculosis. Thus, under conditions of rest, and following nephrectomy when there is coincident urinary tuberculosis, the hard and craggy epididymis may shrink and resolve. It is in this type of case that regular re-examination with or without the employment of tuberculin may be particularly useful. In a more resistant form or when a scrotal sinus remains open, a localised epididymectomy may be carried out with minimal disturbance to testis and cord A local and restricted softening with caseation may be treated by aspiration alone. Massive caseation with the formation of a cold abscess, or accompanying orchitis requires more radical operative interference At the operation involvement of the scrotal skin may be dealt with by excision, but whether the epididymis is to be removed alone or the testis along with it must be left to the judgment of the operator. When the testis is involved, or when the free excision of epididymis, associated abscess, and adherent and infected vas deferens as far as the inguinal ring may have deprived the testis of its blood supply, there is no alternative to orchidectomy. The desirability for the preservation of one testis for the sake of its internal secretion, as well as for psychological reasons, is sufficiently commendable when it is remembered that, in spite of an epididymo-orchidectomy on the first appearance of tuberculosis in the genital system, the disease may break out in the remaining epididymis and testicle after months or even years have intervened. Again, the question of conservatism *versus* radical removal must come up for consideration, but under circumstances demanding a still more thoughtful judgment and careful decision. Occasionally, tuberculous urethritis followed by stricture may be found as a sequel to genital tuberculosis. In this condition peri-urethritis and multiple sinuses and fistulæ in the perineum may lead to great suffering and distress. I have had the opportunity of observing two cases with this complication of genital tuberculosis, and in both the urethroscopic examinations at the outset were made in association with the late David Lees. The patients were young men who had undergone unilateral orchidectomy for

tuberculosis. In both a urethral discharge developed and tubercle bacilli were isolated. Stricture appeared after a short interval, but in the one general treatment and occasional dilatation by bougies seemed to bring about a complete quiescence and cure. In the other, five years after orchidectomy, the stricture became impermeable and perineal fistulæ were leading to serious ill-health and misery. Following suprapubic cystostomy and complete rest in bed in the sanatorium the general condition improved and some two years later this patient was able to move about, but with great inconvenience from constant urethral spasm and a perineal discharge. The tuberculous process had now extended to the prostate. The upper urinary tract was healthy as far as could be determined by intravenous urography, and accordingly both ureters were transplanted to the bowel. Now, five years after ureteral transplantation and ten years after the appearance of tuberculous urethritis, this man has complete control of urination per rectum at normal intervals and, aged thirty-three years, he is able to earn his living as a labourer. Yet his history seems to illustrate the essential value of rest, general and local, in the management of urogenital tuberculosis.

Summary of Treatment

The standard of rest is that practised by the sanatorium physician in the management of all lesions of focal tuberculosis wherever they may be. In the urinary tract the part played by the tuberculous kidney is that of an organ of excretion which never heals, and constantly disseminates infection to the bladder Renal tuberculosis is treated by nephrectomy and the object of the subsequent treatment is to enable the ulcerated bladder to heal. The after-treatment requires to be continued for at least six months under a sanatorium regimen. If, in spite of adequate post-operative care, persistent ulceration of the bladder with contracture, leads to backward pressure on the remaining kidney, such as will endanger its reserve, cutaneous ureterostomy offers a form of relief which is both effective and long-standing.

A conservative outlook should be adopted primarily in the treatment of genital tuberculosis

In combined urogenital tuberculosis, if operative treatment is permissible on general grounds, the major source of infection and reinfection in the urinary tract should be dealt with by removal

of the diseased kidney, and thereafter the genital lesions are treated as their response to general rest may determine.

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PROSTATIC ENLARGEMENT

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Prostatic Enlargement

THIS lecture is based on my personal experiences in the treatment of this condition, those of a general surgeon with a special interest in urology.

It would be undesirable to spend time in a detailed description of the clinical features of prostatic enlargement, as you are no doubt already familiar with these. I have, however, analysed a short series of private and hospital cases under my personal care in recent years under these headings, viz. (*a*) the initial symptoms, (*b*) the cause of the first consultation with the family doctor, (*c*) the reason for surgical advice being sought by patient and doctor.

Total cases reviewed, 110; private 56, hospital 54. The youngest patient was aged forty-nine and the oldest eighty-six.

	Frequency	Retention	Bleeding	Weakness	Pain
Initial symptoms	82	20	6	1	1
Symptoms at first visit to doctor	51	51	8	.	.
Reasons for reference to surgeon	40	60	10		.

Except in patients where the initial symptom has been urinary retention, the interval between first symptoms and first visit to family doctor has been between two or three years.

The interval between initial visit to doctor and first surgical consultation has been as a rule a matter of weeks or months in those who have consulted the doctor for frequency, the interval being longer in private patients, who have been treated by rest and various diuretics and urinary antiseptics Patients with retention of urine as a rule find their way speedily to hospital; but many patients, both hospital and private, have had regular

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catheterisation for a month or more in the hope that surgical treatment may be avoided.

The above table shows the increasing incidence of retention as compared to frequency when the patient reaches the surgeon, and the comparatively small increase in the number of patients suffering from hæmorrhage. These observations go to prove that the present attitude both of patients and doctor is to postpone surgical interference. The patient feels that he is suffering from a condition which is inseparable from advancing years, and that he must make the best of it, and is unwilling to submit to operative interference, firstly on the ground that the operation is a serious one and attended by a definite mortality, and secondly because he has heard that many of his friends who have been operated on have found the convalescence unpleasant and trying. The doctor often hesitates to encourage the patient to consult a surgeon because he is afraid of the mortality risk, and he hopes the operation may be postponed as long as possible. This is fallacious reasoning, because the earlier the patient sees the surgeon the less is the risk, and the shorter the period of disablement.

Patients suffering from prostatic enlargement may, from the surgical point of view, be grouped as follows :—

(*a*) Those with retention of urine : (1) acute retention ; (2) acute retention supervening on chronic retention.
(*b*) Those without retention of urine.

I have placed the groups in this order because, as we have seen, those with retention predominate.

Patients with Retention of Urine

These have been divided into two sub-groups, and I regard this subdivision as important.

An elderly man may have a moderate prostatic enlargement with slight nocturnal or diurnal frequency, and may suddenly become the victim of acute urinary retention. This is due to congestion of the prostate, the immediate exciting factors being chill, and failure to empty the bladder timeously whether from lack of opportunity or from neglect due, for example, to intoxication. The immediate treatment of this condition should be by a hot bath and morphia suppository to relieve the congestion.

Should this fail, catheterisation with a rubber catheter may be carried out, and frequently the relief given by reducing the volume of urine in the over-distended bladder is sufficient to re-establish normal micturition. It may be necessary, however, to pass the catheter on several occasions, or to employ it once daily, preferably in the evening, to prevent further over-distension. Operative treatment is not always required in these patients—the actual prostatic enlargement may be slight and the congestive element great. One patient, aged sixty-five, suffered from acute retention in 1937 and required catheterisation for several days, but he can still hold his water for several hours and has no symptoms of discomfort. He has not required an operation and presumably the prostate has not further enlarged. The patient, however, should not be allowed to discontinue medical attention without complete investigation to decide whether or not operative treatment of the enlarged prostate is desirable

Acute urinary retention supervening on chronic retention presents an entirely different picture There has been gradually increasing frequency of micturition with a smaller and less forcible stream, till overflow dribbling has given place to complete inability to pass urine. There is marked constitutional disturbance with a dry coated tongue, exhaustion from lack of sleep, mental apathy, and a carelessness with regard to personal appearance. His relatives may have noted these latter symptoms without suspecting the cause, and have ascribed them to failing health from old age. Uræmia may threaten.

It has long ago been pointed out that this condition must be relieved by *gradual* decompression of the obstructed urinary tract. The enthusiastic house surgeon who proudly informs you that he has drawn off three or four pints of urine has long had his views on this matter corrected. On the other hand, the surgeon has too frequently failed to realise that it is just as fatal to withdraw the urine rapidly by inserting a suprapubic drain and allowing the bladder to empty completely

There have been various expedients to permit of the slow evacuation of the bladder—the use of a very fine catheter, even of a ureteric catheter has been advocated Frank Kidd recommended a U-siphon tube which has proved effective Hamilton Bailey[1] describes Kidd's method, and emphasises the need for control of the bladder distension by allowing the suprapubic tumour to shrink by not more than one finger-breadth per diem, the level being checked by skin markings

Latterly, we have employed the regulator from the intravenous drip apparatus, inserting it between the catheter and the tube leading to the bedside receptacle, and we find this a very satisfactory method of controlling the outflow. The complete reduction of the bladder tumour requires from five to seven days. During this time the general condition of the patient improves, the best index of the improvement being given by the condition of the tongue.

In cases where a catheter cannot be introduced *per urethram* and tied in, a suprapubic tube may be introduced, but controlled drainage must be maintained. Should the bladder empty too rapidly, Bailey recommends the introduction of normal saline to increase the intravesical pressure, again gauging the amount by the level of the fundus on the abdominal wall.

The danger in these patients is that rapid evacuation of the bladder will convert a post-renal anuria (retention of urine) into a renal anuria (suppression of urine) and precipitate uræmic symptoms.

Patients without Retention of Urine

The first essential is to establish the diagnosis of simple prostatic enlargement. It may be simulated by vesical or prostatic calculi, by median-bar hypertrophy, and by malignant disease of the prostate, while the possibility of a urethral stricture must not be forgotten even in the elderly. In the majority of patients the correct diagnosis will be suggested by rectal examination. Should there be general enlargement of the gland of moderate or soft consistency, but not necessarily uniform increase of each lobe, diagnosis may be regarded as certain Should the prostate be very hard in consistence, malignancy may be suspected though hardness may be due to the presence of true prostatic calculi or calculi in the prostatic urethra, both varieties being demonstrated by X-ray examination A small, firm, but not densely hard prostate should suggest median-bar hypertrophy Cystoscopic examination should be carried out in all patients when the prostate is not found enlarged on rectal examination. This will reveal the presence of intravesical projection of the lateral lobes or the enlargement of the middle lobe. In " prostatism without prostatic enlargement," or as it is better termed, median-bar hypertrophy, the characteristic prominence of the inter-ureteric bar and its increased curve towards the urethral orifice will confirm the

diagnosis. Cystoscopic examination should be carried out in all patients with hæmaturia as a complicating vesical papilloma or carcinoma may be present. In general, however, cystoscopic examination should be avoided except for the special purposes just mentioned.

Having decided that there is a benign enlargement of the prostate the surgeon must consider whether operation is indicated and, if so, what the nature of the operative procedure should be.

Operation is required to relieve urinary obstruction. The criterion of urinary obstruction is the measurement of the residual urine. Should this exceed 2 oz. then operative treatment for the relief of obstruction is desirable. The risk of the operation must be weighed up. The efficiency of the circulatory and respiratory system and of the central nervous system must be estimated, and the surgeon must satisfy himself that the condition of any or all of these does not constitute an unduly serious operative hazard. Thomson Walker[2] points out that tabes dorsalis does not prevent successful prostatectomy. A quantitative and qualitative examination of the urine is carried out. Renal function may be estimated by various tests such as urea concentration, estimation of the blood urea, urea clearance test, or intravenous urography. Each surgeon has his own particular preference I use the blood urea nitrogen estimation, the blood being collected before breakfast. The upper limit of safety is 50 mg., or preferably 45 mg per 100 c.c. of blood. Such tests are not of themselves an indication of fitness for operation, but a patient apparently fit for operation on clinical examination may be shown to have defective renal function. The urea clearance test is too elaborate for routine clinical work. Intravenous urography is of value in patients with a border-line urea figure

Preliminary Drainage of the Bladder

In all but a few patients this will be found necessary. The value of preliminary emptying of the bladder by regular catheterisation has long been recognised even before its exact purpose, namely, to improve the renal function, was noted

In many clinics preliminary cystostomy and a two-stage operation is the rule. I regard this as undesirable for two reasons, firstly, because in my opinion the psychological effect on the patient is bad when a minor operation precedes a major one, the patient being apprehensive of the possibilities of the larger;

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incompetence following operation. Threatened renal anuria can be relieved by the prompt intravenous administration of an isotonic aqueous solution of sodium sulphate (Wade and Dick[3]).

Control of Hæmorrhage

An appreciable number of patients formerly died of shock due to hæmorrhage. The measures taken to prevent this varied. Freyer advocated firm digital pressure exerted on the prostate bed after the enucleation had been completed. Other surgeons relied and many still continue to rely on packing the prostatic cavity with gauze. Its removal is painful and it tends to produce sepsis Others advocate irrigation with hot lotion Hydrostatic bags, notably Pilcher's bag, have been used (Millar[4]) In my experience this is not well tolerated by the patient. Thomson Walker[5] demonstrated the desirability of an open operation, using a retractor to expose the prostate bed after enucleation with the purpose of removing tags of tissue, enlarging the upper rim of the cavity to prevent post-operative stenosis, and securing the bleeding vessels in the upper rim of the cavity by suture. In the hands of the expert operator this does not materially add to the duration of the operation. S. Henry Harris[6] proposed an operation with complete closure of the bladder. He used hæmostatic sutures similar to those of Thomson Walker, but instead of enlarging the upper opening of the prostate bed he used a boomerang needle inserted under direct vision above the centre of the inter-ureteric bar and carried behind the prostate bed to pick up the lower edge of the capsule. A catgut suture thus inserted was tied and brought the trigonal flap down to cover the posterior raw surface of the prostate bed. He then inserted two sutures transversely to approximate the lateral edges of the prostate bed over a catheter passed *per urethram.* He differed from most surgeons in opening the bladder empty and not previously distended, and in paying special attention to ligating any vessels in the bladder wall. He claimed that hæmostasis was so perfect that he could close the suprapubic wound and rely on catheter drainage alone, the urethral catheter being retained by means of a silkworm gut stitch brought out through bladder and parietal wound and tied over a glass rod attached to the skin. When it is desired to remove the catheter the suture is divided at the level of the skin and the deeper portion is withdrawn through the urethra with the catheter.

and secondly, because the convalescence after a one-stage operation can be made much more comfortable than after a prostatectomy, when preliminary cystostomy is required. I reserve the two-stage operation for patients whose blood urea remains consistently high, for those where catheterisation is difficult or impossible or causes hæmorrhage, and for those who have already developed a severe cystitis. In a patient with average health, reasonably clean urine, and a blood urea of, say, 60 to 70 mg. per 100 c.c., drainage by urethral catheter is preferred. Twice daily the bladder is washed out with weak boracic lotion, using a Carrell syringe to instil and siphon back the lotion. This prevents stagnation of urine in the retro-prostatic pouch.

Operative Treatment

When the patient is thus rendered fit for radical operative intervention, three procedures are available :—

1. Suprapubic prostatectomy.
2. Perineal prostatectomy.
3. Transurethral diathermy resection.

Perineal prostatectomy has been advocated chiefly by American surgeons and has found little favour in this country.

Transurethral diathermy resection either by the McCarthy instrument or by the Thomson punch has many advocates. It was at first hoped that the use of such methods would enable radical operations to be performed on patients whose physical condition and urinary function did not reach the required standard. One advantage of this method is that the period of stay in bed and in hospital is diminished, and that much of the discomfort of convalescence is eliminated

Suprapubic prostatectomy has remained the operation of choice in my practice. The essential factors for success in this procedure are :—

1. Prevention of urinary failure.
2. Control of hæmorrhage.
3. Minimal discomfort for the patient during convalescence.

Prevention of Urinary Failure

Despite the pre-operative investigation and treatment already set out, a certain number of patients may show signs of renal

Retzius. With a Carrell syringe boracic lotion is introduced through catheter and suprapubic tube and sucked gently back to extract any clots. The patient is returned to bed and the catheter and suprapubic tube drained into bedside bottles.

After-Treatment

General.—A moderate degree of primary shock follows the operation, but speedily passes off when the patient is returned to bed and radiant heat is applied. Rectal infusions are contra-indicated, and intravenous drip and blood transfusion are required only in the very rare cases of secondary shock. Blood transfusion must be used with caution. It may raise the blood pressure in the kidneys and interfere with their function, and may even precipitate renal anuria

Local after-treatment is important. Continuous suction drainage is not available in my wards. For a time I used a Cathcart-Sprengel drainage, later this was combined with intermittent irrigation with weak boracic lotion, but for some years past suction irrigation with a Carrell syringe has been employed. In the first twenty-four hours this is reduced to a minimum, being used only to clear the tube and catheter of clots, but thereafter, when the risk of reactionary hæmorrhage has passed, it is regularly carried out every four hours. It will be found that débris of clot and prostatic tissue are easily aspirated and the interior of the bladder kept clean. On the fourth day the suprapubic tube and parietal drain are removed. This may be the first dressing required, though in some cases there is leakage of urine round the suprapubic tube in the first twelve hours, necessitating change of dressing at that stage. It is found that, if the suprapubic tube is then removed, the risk from reactionary hæmorrhage is over, while the edges of the bladder wound remain sufficiently pliable to fall together, and that leakage from the suprapubic opening is minimal. To achieve this a one-stage prostatectomy through the intact abdominal wall is essential. Preliminary suprapubic cystotomy leaves an indurated track in the parietes and the bladder wall which does not collapse and permits continuous leakage. In such patients, if the bed is to be kept reasonably dry, the use of a Hamilton Irvine box is essential. The urethral catheter is removed on the tenth day, by which time the suprapubic wound is healed except for a small granulating area where the tube was inserted. The patient commences to

Attempts to check post-operative hæmorrhage by diathermy coagulation have not proved satisfactory as there has been a tendency to sloughing with reactionary or secondary hæmorrhage

Post-operative Comfort

The original Freyer suprapubic tube was of large calibre, often an inch in diameter. After its removal a large suprapubic wound was left from which copious leakage occurred, minimised but not relieved by the insertion of a urethral catheter. In the ideal primary closure the danger of a certain amount of reactionary hæmorrhage cannot be eliminated, and my preference has been for the use of a suprapubic tube of moderate calibre for a short time after operation.

Operative Technique

A brief description of the steps of the operation as personally performed is given.

After pre-medication with omnopon gr. $\frac{1}{3}$ and scopolamine gr. $\frac{1}{150}$, general anæsthesia (gas and oxygen) is employed, though in a certain number of patients, especially those with a bronchitic tendency, spinal anæsthesia (hypo-baric percaine) has been used

The bladder is filled with 10 oz. of boracic lotion. A vertical midline suprapubic incision is made. This should be long enough to permit the surgeon's hand to pass between the recti muscles, enabling him to enucleate the gland without the necessity of putting a finger in the rectum. A stitch of catgut is passed through the bladder wall and acts as a tractor. The bladder is incised and the fluid removed by suction. Any bleeding vessels in the bladder wall are secured by forceps and tied. The prostate gland is enucleated, and the cavity temporarily packed with a gauze swab. Morson's illuminated self-retaining retractor is then inserted. Loose tags are cut away. By means of the boomerang needle Harris's lateral hæmostatic sutures and trigonal suture are inserted and tied, Morson's forceps being used to catch the lower edge of the prostatic capsule The field is now practically bloodless A rubber catheter (size 20 French) with lateral openings is introduced into the urethra. The eye of the catheter lies in the bladder, and the lateral openings in the prostate bed The catheter is retained by Harris's method. The bladder wound is closed round a Winsbury-White suprapubic tube (size 28 French) and the parietal wound closed with a small drain to the space of

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pass urine *per vias naturales*, and he is allowed to sit in a chair from the twelfth day when stitches are removed. Within three weeks of the operation he is able to go about freely. Frequency of micturition persists up to about six weeks after the operation, probably from reflex bladder spasm, as complete epithelialisation of the prostate bed does not take place before that time.

It has been possible on two occasions to inspect the bladder at operation a considerable time after the removal of the prostate. The cavity has become funnel-shaped and is completely epithelialised.

During the convalescence the urine remains almost clear. The patient is encouraged to drink bland fluids freely, and after the suprapubic drain is removed, a six-day course of Collosol Mandelate (Crookes) is frequently of value. This, unlike some other mandelic preparations, is well tolerated.

In patients with two-stage prostatectomy the convalescence is longer on account of the delay in healing of the parietal wound, and the Hamilton Irvine box is not always comfortable.

Much has been written of the disadvantages of the indwelling urethral catheter. I have never seen persistent urethritis caused. There is often some discharge at the meatus alongside the catheter, but this comes from the unhealed prostate bed, and is reduced to a minimum by the aspiration-irrigation technique above described The catheter performs a similar function to the perineal drainage tube described by Fullerton [7]

It is claimed for this operation and after-treatment that the discomfort of the patient is reduced to a minimum, that the absence of soakage of the dressings and bed have not only lightened the tasks of the nursing staff, but have effected a very substantial economy in dressings and laundry costs. Lumb [8] and Morson [9] have described an operative technique on similar lines, the former recommending a two-stage operation with preliminary cystostomy.

Complications following Operation

There had been a certain incidence of epididymitis This is not only painful but delays convalescence. Formerly division of the vas deferens was not carried out, but it is now practised in the majority of cases with successful results in the prevention of this complication.

Chest complications are rare, spinal anæsthesia being used

in patients who have an obvious bronchitic tendency. There is always the risk of sudden cardiac failure in the elderly patient following a major operation, which cannot be eliminated even by the most scrupulous care in selection and preparation of patients for operation. Pulmonary embolism may occur.

Hæmorrhage has not occurred except in slight amount in the first few hours, and it has been readily checked by hæmoplastin. Only in one patient of the series reviewed has a blood transfusion been required, one pint being given by the drip method.

Conditions complicating Prostatic Enlargement

Vesical or prostatic calculi may be present, the former developing in patients where a long interval has elapsed between a preliminary cystotomy and a subsequent prostatectomy. They are due to a staphylococcal cystitis and are phosphatic. Removal of the prostate with the stone, when the condition of the patient permits, will cure the cystitis.

Simple papilloma of the bladder may complicate prostatic enlargement. The primary symptom is hæmorrhage, and the need for cystoscopic examination of these patients has already been mentioned. In one patient a malignant vesical tumour developed two years after a successful prostatectomy.

Palliative Procedures

Where primary one-stage prostatectomy is impossible, suprapubic cystostomy may be performed. It has been my practice to do this by a "blind" stab operation under local anæsthesia, using Cantlie's trocar and cannula and introducing a de Pezzer catheter through the cannula.

Indications for this operation are :—

1. A persistently high blood urea in patients otherwise apparently fit for prostatectomy. Drainage is continued for a short or long period, the patient being allowed to go about. If and when the blood urea drops to safe limits prostatectomy is then performed.
2. Unsatisfactory general health making prostatectomy impossible. With care the patient can go about in considerable comfort wearing a suitable retention appliance by day, and allowing the suprapubic tube to drain into a bedside bottle by night. Regular bladder

lavage combined with suction by a Carrell syringe will keep the bladder clean and prevent phosphatic deposit.

3. Inability to pass a catheter or complete retention necessitating catheter life will call for cystostomy. About half these patients die from renal insufficiency within the first month. Only rarely can prostatectomy be performed.

Radio-therapy.—The use of X-rays of varying potency has been advised as a means of reducing the prostatic enlargement. While on purely clinical grounds some success is recorded; it is probable that the enlargement was congestive rather than hypertrophic. Recently a patient on whom cystostomy was performed for retention due to presumed malignant prostate, and who had had successive X-ray exposures for nearly two years, required operation for removal of a portion of Pezzer tube which had broken off. At the operation the prostate was found to be very large but soft. It was successfully enucleated and proved on microscopic examination to be non-malignant. Prolonged X-ray therapy had in no way reduced its bulk.

Steinach Operation I and II.—I have not personally performed either of these, but have seen patients who had undergone them without benefit.

Malignant Disease of the Prostate

The patients in a period corresponding to that over which the 110 simple cases were observed numbered 11, mostly over seventy years of age. One patient was regarded as a simple enlargement. His symptoms were retention for two days. The microscope showed the presence of adeno-carcinoma. He rapidly went downhill after operation and died in five days Only six patients came on account of urinary trouble, one with frequency, four with retention, and one with hæmaturia The history of previous urinary trouble was always of brief duration except in the case of one patient, aged eighty-six, who had cystotomy for retention four years previously and returned with the opening blocked by a fungating mass. He had removed the suprapubic tube and refused to have it replaced, and for a time had passed all his urine *per urethram.* One patient had normal urine and no urinary symptoms, but complained of difficulty in moving the bowels and had a large hard prostate projecting into the rectal ampulla.

Two patients were referred on account of sciatica. One had slight frequency, and metastatic deposits in the pelvic bones were

seen on X-ray examination. The other developed retention, when under medical treatment for sciatica in a nursing home. The prostate was found to be hard and moderately enlarged. Cystostomy was performed. X-ray examination showed extensive metastasis in the vertebral column, ribs and pelvis, also in both femora.

In two patients pain in the back was followed by paraplegia, and it was on account of the nervous lesion rather than of the prostatic enlargement that retention occurred.

Prostatic cancer is of slow development. Evidence of its occurrence, viz. a slight enlargement and stony hardness of the prostate, was discovered during rectal examination in investigating dyspepsia in a man of sixty. No treatment was carried out, and it was over five years till he developed a sudden retention of urine. Comparative latency of symptoms of carcinoma of prostate agrees with findings of McGavin.[10]

Treatment of this condition is unsatisfactory. Of operation for complete removal in the early case I have no personal experience. It is a formidable procedure.

The value of X-ray therapy is doubtful. Some radiotherapists claim successful results, others decline to treat the patients on the ground of non-success. Both surgeon and radiotherapist are agreed that the pain of secondary lesions in bones can be greatly alleviated by X-rays.

Radium therapy by implantation of needles has proved disappointing. In many patients its only result has been to provoke early fungation of the growth with its attendant miseries.

Trans-urethral electro-resection may relieve retention but is pathologically unsound, as it destroys the natural barrier and allows the growth to fungate

My best results as far as the patients' comfort goes have been from pre-sacral neurectomy carried out simultaneously with cystostomy, and subsequent X-ray therapy to reduce the pain from metastases.

Results

Patients submitted to suprapubic prostatectomy remain comfortable. They can lead an ordinary active life Diurnal and nocturnal frequency disappear and the normal size and force of the urinary stream is restored. Destruction of the internal sphincter leads to sterility as the semen passes backwards into

lavage combined with suction by a Carrell syringe will keep the bladder clean and prevent phosphatic deposit.

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A method of pre-operative, operative and post-operative management designed to reduce the risk and discomfort of the operation has been described.

Malignant disease of the prostate causes few urinary symptoms and is of slow growth. Its treatment is unsatisfactory as most patients present themselves with symptoms of secondary dissemination of the growth.

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the bladder and is not retained in the posterior urethra and ejaculated (Macalpine).[11] Mortality from primary one-stage prostatectomy is low. In the last twenty private patients thus operated upon one death has occurred. This patient was non-co-operative and convinced from the first that he would not survive the operation. When two-stage prostatectomy has been carried out in twelve private patients over a corresponding period five patients have died. Three patients, aged seventy-five, eighty-four and eighty-six, all demanded operation as they found the suprapubic tube irksome after a few weeks trial. They all appeared to be fit both in general health and urinary function to undergo the major operation with a reasonable prospect of success; they succumbed to myocardial failure. Of the remaining two, one died of pulmonary embolism, and one of uræmia. The latter patient had a phosphatic stone and a border-line blood urea, and it would probably have been better merely to remove the stone and postpone prostatectomy.

In the last twenty hospital patients submitted to one-stage prostatectomy, three deaths have occurred, one from syncope twenty-four hours after the operation, one from hypostatic pneumonia, and one some weeks after the operation from an obscure nervous degenerative lesion, the prostatectomy wound having healed satisfactorily, but the patient still remaining in hospital. In the same period eight patients had two-stage prostatectomy with one death from post-operative collapse, probably cardiac, as there was no excessive bleeding. Morson, in the paper already quoted, draws attention to the variable results obtained from statistics drawn from comparatively small groups of patients. A follow-up of private patients successfully operated on in the past few years has shown them to be entirely free from urinary discomfort, and none of them has suffered from post-operative stricture

Summary

Patients with symptoms of enlarged prostate fail timeously to consult doctor and surgeon.

Fear of the risk and discomfort of operation is probably the most common cause of delay.

About half the number of patients reaching the surgeon in hospital or private practice are unfit for prostatectomy.

Suprapubic prostatectomy remains an operation of choice.

The cases in this series were all male, and the average a was sixty-five years At the risk of being somewhat monotonoı I would like to give you brief summaries of their histories, they illustrate well a number of the complications of the conditio I present the series to you in chronological order, with all tl inadequacies and inconsistencies of treatment for which n incomplete understanding of the importance of the conditic must be blamed. Diverticulum may not have been the chi condition in all the cases, but at least it was an important cor plication. As a general surgeon who has to deal with cases c acute retention and prostatic obstruction, I feel my experienc could be passed on to you with profit.

Summary of Case Histories

CASE 1. 1931.—66-year-old man with a frankly malignant prostate, died in 3 weeks At P.M. intraperitoneal perforation of bladder diverticulum found Diverticulum contained six round calculi Spheroidal cell carcinoma of prostate with secondaries in pelvic lymph glands.

CASE 2 1931.—A carpenter, 66 years of age, had acute retention One-stage prostatectomy done. Prostate had middle lobe collar Two diverticula containing many small stones felt in left side of bladder. These diverticula were not touched Two weeks after operation had sudden discharge of foul blood-stained urine, and next urine was clear. Died 6 years later of senility

CASE 3 1932.—Retired Eastern banker, 73 years of age, had three attacks of hæmaturia A small diverticulum was present above right ureteric orifice Pyelograms normal Incidental cystogram obtained Ten years later cystoscoped again for hæmaturia, and blood was seen coming from left ureteric orifice Uroselectan showed incidental cystogram, and shows diverticulum slightly larger and more globular There was no obvious bladder neck obstruction in this case.

CASE 4 1933—A farmer of 70 years had retention of urine for a week. Cystoscope would not pass. Suprapubic cystostomy done, and then later an endoscopic resection Five years later returned with hæmaturia. Cystoscopy showed cystitis and openings of three diverticula. No cystogram taken Cystitis cleared up. Returned in another 5 years at age of 80. Blood urea 159 mgs per cent. Died two days later. The

DIVERTICULUM OF THE URINARY BLADDER

By A. J. C. HAMILTON, M B, F.R.C.S.Ed, F.R C.S.Eng.
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In British surgical literature very scant attention has been paid to diverticulum of the urinary bladder. I can only find three series of cases published. In 1923 Swift Joly reported a series of 14 cases to the Royal Society of Medicine. In 1925 Ogier Ward published a series of 11 cases in the *British Journal of Surgery*, bringing the series up to 53 in 1938. Apart from these series only isolated cases have been reported in this country.

In America, on the other hand, from various urological clinics, many series of cases have been published, the largest series being 236 cases by Kretschmer of Chicago in 1940.

Giving rise to no characteristic symptoms or clinical signs, its diagnosis rests exclusively on cystoscopy and cystography—this perhaps explains its elusive nature. I feel that many cases of diverticulum remain undiscovered, and that persistent urinary infection and the occasional unsatisfactory results of the operation of prostatectomy or of suprapubic cystostomy may be due to the presence of an unsuspected diverticulum

Henry Wade in his teaching always insisted on the importance of routine cystoscopy in cases of prostatic obstruction, and the occasional discovery of an associated papilloma, calculus or diverticulum only confirmed how sound this teaching was

This series consists of 22 cases encountered during the last sixteen years. Eighteen of these cases were treated in the Royal Northern Infirmary, and during that period there were 280 in-patient cases of prostatic obstruction under my care. This gives an incidence of one case of diverticulum in every 15·5 cases of prostatic obstruction. I think the incidence of diverticulum is probably greater than this as, firstly, in many of the 280 cases no cystoscopy was done and no cystogram was taken and, secondly, 12 cases of diverticulum were seen in the last four years when the condition was being definitely looked for.

Read 10th June 1943

Diverticulum of the Urinary Bladder

The cases in this series were all male, and the average age was sixty-five years. At the risk of being somewhat monotonous, I would like to give you brief summaries of their histories, as they illustrate well a number of the complications of the condition. I present the series to you in chronological order, with all the inadequacies and inconsistencies of treatment for which my incomplete understanding of the importance of the condition must be blamed. Diverticulum may not have been the chief condition in all the cases, but at least it was an important complication. As a general surgeon who has to deal with cases of acute retention and prostatic obstruction, I feel my experience could be passed on to you with profit.

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only things to note about this case were that he had no treatment for his *diverticula, and had persistence of urinary infection for 10 years*

CASE 5. 1934.—A camp superintendent of 66 years had a 6 weeks' history of passing bright red blood in his urine in quantity. Cystoscopy showed a fenestrated bladder of reduced capacity, with several diverticula, chief one above the right ureteric orifice. A cystogram was taken. At operation a diverticulum was felt fairly far back, with a friable tumour in it. Diverticulum and tumour were excised by cutting through bladder wall to orifice of diverticulum Tumour was a malignant papilloma. *Four months later*, on cystoscopy, bladder capacity was normal, and no evidence of recurrence. Died 7 months after operation in Ayrshire; cause unknown.

CASE 6. 1937.—A church organist of 58 years, with a year's history of a quick call to micturition. Doctor found a distended bladder and withdrew 52 oz. of urine by catheter. Admitted passing blood-stained urine, suggesting a renal origin Blood urea 121 mgs. per cent. A suprapubic cystostomy was done. A large diverticulum was felt *posteriorly, occupying most of back wall of pelvis No marked prostatic* enlargement. Developed a solid œdema of both legs. Was re-admitted 8 months after first operation and diverticulum excised It was a difficult operation on account of many adhesions Twenty days later developed a femoral thrombosis, and a week later died of mesenteric thrombosis

CASE 7. 1938.—An ex-Provost of a small town, 76 years, stout, kyphotic, who had had a transient cerebral hæmorrhage a year before, gave a history of 2 months' hæmaturia. Died suddenly, and at post-*mortem an intraperitoneal perforation of a thin-walled bladder diverticulum* was found. A papilloma was found at right ureteric orifice. Two other diverticula were found, one on each side of bladder.

CASE 8. 1938.—A post-office worker, 54 years of age, admitted difficulty in passing water for a number of years. Water came slowly and he had to strain. Palpable bladder—32 oz withdrawn with catheter. Cystoscope would not pass. Hæmaturia developed. In embarking on a one-stage prostatectomy, a large diverticulum was found in right side of pelvis—it was larger than bladder itself; was removed by extra-peritoneal dissection. Middle lobe of prostate also removed; remainder of prostate was firm Has only been off work for one half-day in 4½ years, and keeps very well.

CASE 9 1939.—A blacksmith, 61 years of age, gave a 7 years' history of dysuria and difficulty in micturition, and an attack of retention On cystoscopy a diverticulum was seen and confirmed by cystogram Was sent home, and to return in 3 months for re-assessment. The war came, and I did not see him for 3 years, when he was sent in very ill.

Blood urea rose to 156 mgs. per cent., and pus and blood present in urine. Died in coma. No post-mortem obtained. This case should have been dealt with when first seen (Fig. 1)

CASE 10 1939.—A music-seller, 64 years of age, gave a year's history of nocturnal frequency and difficulty in passing water A posterior diverticulum was seen on cystoscopy and in lateral cystogram. Diverticulum and prostate with a large middle lobe collar were removed at one stage. Diverticulum filled large part of right side of pelvis. Is well 3½ years after operation.

CASE 11. 1940.—A labourer, 60 years of age, gave a history of 3 months' difficulty with micturition. A diverticulum of right side of bladder was seen on cystoscopy At operation diverticulum was removed; prostate was too fibrous to enucleate. Prostatic urethra was dilated with finger. Has been keeping well. When examined recently had 3 oz. of residual urine. Will probably require an endoscopic resection of prostate.

CASE 12. 1940.—A retired army colonel, 66 years of age, had dysuria and frequency On cystoscopy, diverticulum seen above right ureteric orifice. Diverticulum and prostate removed at one stage Keeps very fit over 3 years after operation (Fig 2).

CASE 13 1941.—A large, stout, one-legged man, 67 years of age, gave a history of 13 years' dysuria. On cystoscopy, foul-smelling urine withdrawn. No good view of bladder obtained in spite of repeated lavage. A suprapubic drainage was done, and bladder explored with the finger which went easily into a diverticulum on right side of bladder Developed a cellulitis of loin, and died from septicæmia 16 days after operation No post-mortem was obtained.

CASE 14 1941 —A shepherd, 70 years old, gave a history of 3-4 years' inability to control urine. Cystoscopy showed a diverticulum behind right ureteric orifice Blood urea 65 mgs. per cent A suprapubic cystostomy was done. A year later prostate was removed, but diverticulum not noticed at operation Had a lot of bleeding after operation. Returned 7 months later with hæmaturia. Died 3 months later from ascending infection.

CASE 15 1941 —A captain in Merchant Navy, 57 years of age, developed acute retention 6 days before admission. Five months before this had noticed a hesitancy in micturition followed by dribbling On cystoscopy two diverticula were seen Cystogram showed large diverticulum on right side of pelvis—smaller on left. Diverticulum on right side (which was larger than a closed fist) was removed along with the prostate in one stage. He remains well, and is back on Atlantic convoy work (Fig. 3).

CASE 16. 1942.—A lumberjack, 50 years old, gave a 3 months' history of difficulty in starting micturition and difficulty in passing urine. Pyelography showed dilatation of left renal pelvis without any clubbing of calyces. At operation diverticulum found to be adherent to a somewhat dilated ureter. Diverticulum was excised. No enlargement of prostate was present, only a slight marginal thickening of the internal meatus. This was easily dilated with the finger. The hydronephrosis appeared to be due to the adherent diverticulum. When last seen, 10 months after operation, he was well and working full time (Fig. 4).



FIG 3—Case 15 Diverticulum removed Note small orifice in centre at X.

CASE 17. 1942—A 70-year-old crofter, 2½ years previously, had had a one-stage prostatectomy done following an attack of acute retention A small diverticulum was noticed in posterior and right part of bladder at operation Admitted on this occasion, he gave a history that he had been perfectly well until 5 weeks before, when he developed severe pain on micturition On cystoscopy and X-ray there were seen to be two calculi, one being in the diverticulum At operation it was found that originally it had been a dumb-bell calculus, one end being in diverticulum. It was only when the "dumb-bell" broke in two the patient had symptoms of bladder stone The diverticulum was a small one, and an attempt to mobilise it was given up, as it was so adherent. He may develop another stone in this diverticulum



(a)



(b)

FIG 1—Case 9 (a) Before Micturition, (b) After Micturition Note how diverticulum has got larger, bladder partially emptied into diverticulum



FIG 2—Case 12 Diverticulogram



FIG 4—Case 16 Showing hydronephrosis and a diverticulum which was adherent to ureter

CASE 16. 1942.—A lumberjack, 50 years old, gave a 3 months' history of difficulty in starting micturition and difficulty in passing urine. Pyelography showed dilatation of left renal pelvis without any clubbing of calyces. At operation diverticulum found to be adherent to a somewhat dilated ureter. Diverticulum was excised. No enlargement of prostate was present, only a slight marginal thickening of the internal meatus. This was easily dilated with the finger. The hydronephrosis appeared to be due to the adherent diverticulum. When last seen, 10 months after operation, he was well and working full time (Fig. 4).



FIG 3.—Case 15. Diverticulum removed Note small orifice in centre at X

CASE 17. 1942—A 70-year-old crofter, 2½ years previously, had had a one-stage prostatectomy done following an attack of acute retention. A small diverticulum was noticed in posterior and right part of bladder at operation. Admitted on this occasion, he gave a history that he had been perfectly well until 5 weeks before, when he developed severe pain on micturition On cystoscopy and X-ray there were seen to be two calculi, one being in the diverticulum. At operation it was found that originally it had been a dumb-bell calculus, one end being in diverticulum. It was only when the "dumb-bell" broke in two the patient [illegible] culum was a small one, and [illegible] was so adherent. He may



FIG 5—Case 18 Diverticulogram in which iodide has overflowed into bladder and shows other diverticula Note calcification of prostate



FIG 6—Case 19 Cystogram showing diverticulum on each side



FIG 7—Case 20 Diverticulogram taken in case with suprapubic tube Rounded head of tube is seen lying in bladder medial to diverticulum Pointing of diverticulum suggests an adhesion is present



FIG 8—Case 21. Lateral cystogram showing posterior diverticulum which has a wide communication with bladder

CASE 18 1942.—An ill, poorly nourished man of 75 years came up to hospital with acute retention. Was relieved by catheterisation. Condition deteriorated, and blood urea rose to 246 mgs. per cent.—looked as if he was going to die of uræmia. He quite suddenly improved, and blood urea came down to 33 mgs. per cent. Cystoscopy showed four diverticula. In the lower right one a whole ureteric catheter could be coiled up. A cystogram showed diverticula, and extreme calcification in his prostate. When last seen six weeks ago was still keeping well (Fig. 5).

CASE 19 1943—A retired able seaman of 67 years gave a 3 years' history of frequency of micturition. Cystoscopy showed a diverticulum above and medial to left ureteric orifice. Prostate and diverticulum were excised at one stage. Died 2 days after operation. Post-mortem showed advanced coronary atheroma, and a large atheromatous ulcer in the aorta. Histology of the prostate showed fibro-adenomatous hypertrophy with an area of adeno-carcinoma at one spot (Fig. 6).

CASE 20 1943.—A painter, 61 years of age, had frequency of micturition for 3 years, difficulty of micturition for 3 months, and dribbling for 2 weeks. On examination a distended bladder was felt, more on left side of pelvis than right. A suprapubic cystostomy was done, and bladder decompressed. Cystoscopy showed openings of three diverticula in one of which only would a ureteric catheter coil up. A diverticulogram was taken. An endoscopic resection of prostate was done (Fig. 7).

CASE 21. 1943—A coastguard of 62 years had a vesical stone removed in 1937. A new stone formed, and this was removed suprapubically, and a diverticulum found which easily admitted two fingers. Cystoscopy after healing showed a large oval orifice situated medial to the right ureteric orifice and depressing the inter-ureteric bar. An endoscopic resection of prostate was done, as there was very little retention in the diverticulum (Fig. 8).

CASE 22. 1943—A retired accountant, 69 years of age, gave a history of intermittent dysuria and frequency for 5 years. Difficulty in starting micturition, and no force when he did pass urine. There was the large oval orifice of a diverticulum medial to the left ureteric orifice, and depressing the inter-ureteric bar. A catheter coiled up in this, but there was very little retention in the diverticulum on account of the wide orifice. An endoscopic resection of prostate was done.

Summary of Treatment in Series of 22 Cases

Diverticulum was removed in 9 cases:

In 4 of these prostate was removed at same time.
In 1 of these middle lobe only was removed at same time.
In 2 of these the prostatic urethra was digitally dilated.
In 2 of these the prostate was not touched.

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Diverticulum was *not* removed in 13 cases.

In 5 of these cases no treatment was carried out.
In 3 cases prostate only was removed.
In 4 cases an endoscopic resection only was done.
In 2 cases suprapubic drainage of the bladder only was done.

Results of Diverticulectomy.—Of the 9 cases where this operation was done, 3 are dead (Cases 5, 6 and 19). The other 6 cases are alive and well.

Three of the cases of endoscopic resection are too recently carried out to assess results

Age.—In this series the youngest patient was fifty years of age, and the oldest seventy-six years. The commonest age of incidence is the sixth decade, a time of life when bladder neck obstruction is common. The fifth and seventh decades are the next most common. (Kretschmer in his 236 cases found 32·2 per cent. in the sixth decade Kutzmann in 100 cases found 42 per cent. in the sixth decade, and de Illeyés in 168 cases found 38 per cent. in the sixth decade)

Kretschmer has seen 9 cases of bladder diverticulum in children, the youngest being twelve days old. These were usually due to congenital valves in the posterior urethra, or to contracted internal urethral orifices

Sex.—I have seen no case in a female Kretschmer in his 236 cases saw 7 cases in females Three of these were due to contracted internal urethral orifices and 3 to extensive carcinoma of the bladder. Schacht and Crenshaw in 1930 reported 18 cases in females, and said the proportion of sex distribution was 3 females to 97 males Urethral caruncles were found in 3 of their cases and a cyst in the bladder neck in another case.

Structure of Diverticulum.—The diverticulum may be thin-walled, or may possess a wall as thick as the bladder itself. Hinman states that in no case is the wall of a diverticulum histologically identical in structure with that of a normal bladder. Several of the diverticula in this series were examined histologically by our pathologist, Dr H J. Kirkpatrick, and his reports show that in some the mucosa is replaced by granulation tissue, outside which is well-formed or dense fibrous tissue. One was lined by stratified squamous epithelium showing hyperkeratosis Muscle tissue is present somewhere in the wall of most diverticula, but varies in amount and condition, often undergoing atrophy and replacement by fibrous tissue.

These diverticula do not have enough healthy muscle tissue to give them any power of contractility. The orifice of communication with the bladder is very small usually in relation to any medium or large-sized diverticulum An exception to this generalisation *occurs in the type of diverticulum found near the* middle line of the bladder posteriorly, where a large, oval orifice may be present which tends to depress the inter-ureteric bar (Cases 21 and 22).

Number of Diverticula.—In 16 cases of this series the diverticulum was a solitary one, and in 6 cases there were two or more diverticula.

Infection—*Of the 22 cases only 4 had urines that were* sterile. The urine of the remaining 18 cases showed pus cells and organisms, and some were grossly infected.

Symptoms.—There are no characteristic symptoms of this condition. The symptoms in this series are those of bladder neck obstruction often combined with those of urinary infection. The most frequent symptom was increasing difficulty in micturition, terminating in 6 cases with acute retention which brought the patient to the surgeon Frequency of micturition was the next most common symptom Hæmaturia was present in 4 cases. No history of *miction en deux* was elicited, although in one case I noticed in washing out the bladder per urethram, the return, which was clear, suddenly became thick and foul, and then quickly became clear again, suggesting a discharge from a *diverticulum Some authors report that patients may find a* change in posture, *e g.* lying on back, facilitates micturition. The duration of symptoms varies greatly, from a day to twenty years

Signs.—There are no characteristic signs of this condition, but the presence of a suprapubic swelling to one side of the middle line should arouse suspicion In one case of the series, *asymmetrical suprapubic distension of the bladder was noticed,* and in another, on rectal examination, an œdematous bulge was felt above the prostate, the diverticulum in the latter case subsequently being found to come from the posterior wall of the bladder It is interesting to note that in this series of 22 cases there were 6 cases of acute retention, and in 4 others a non-tender, distended bladder was felt suprapubically This non-tender distension of the bladder without *overflow incontinence,* where the blood urea is low, should arouse suspicion that a diverticulum is present

Diagnosis

Cystoscopy.—It is only since the routine use of the cystoscope that the relative frequency of diverticulum of the bladder has been discovered. In 3 cases in this series the cystoscope could not be passed through the prostate Sometimes the bladder has to be washed out several times on account of the infection present, before the medium becomes clear enough to obtain a view. In the event of the medium not clearing, a cystogram should be taken.

The most common situation for diverticula is just above and lateral to a ureteric orifice in an area where one often sees the earliest signs of fenestration in an otherwise normal bladder. The orifice of a diverticulum is usually circular, and the dark interior is not illuminated by the cystoscope lamp. MacAlpine describes it as being " Like a hole punched out of the bladder wall. It is generally rounded, but may be slit-shaped, the latter appearance being occasionally due to it being viewed obliquely." The size of the orifice gives no indication of the size of the diverticulum. Often large diverticula have very small orifices —*vide* the largest of these specimens. In fact, I would almost say the smaller the orifice the larger the diverticulum, if the diverticulum in the mid-line posteriorly is excepted, where the orifice is often large and oval. Occasionally the mucous membrane is in folds radiating from the orifice, and several observers have reported sphincteric action of an orifice, so that the orifice may be seen on cystoscopy at one time, and not visible at a second examination The mucous membrane round the orifice may be smooth or may be trabeculated. Usually there is no difficulty in differentiating between a diverticulum and a sacculation. A sacculation is relatively wide-necked and shallow, and partially illuminated, and a ureteric catheter curls out of it at once, or the point of the catheter is arrested at 1 or 2 cms.

Where possible we take a diverticulogram followed by a cystogram.

Diverticulography. — Having discovered the orifice of a diverticulum, one passes in a ureteric catheter. If the whole catheter coils up in the diverticulum an X-ray is taken with the cystoscope still in position. Then a diverticulogram is taken by injecting 20 c.c. of 12½ per cent. sodium iodide along the ureteric catheter. This procedure is especially useful where the diverticulum is on the posterior wall of the bladder, as an

anteroposterior cystogram plate will not show it, and a lateral or oblique cystogram is not always satisfactory. Should the diverticulum be a large one, the 20 c.c. will not fill it completely, but *in this case the cystogram will probably show it up better.*

Cystography. — A *cystogram is* then taken. The *usual* opaque medium we use is 100 c.c. of 12½ per cent. sodium iodide diluted to 300 c.c. with sterile water; 150-200 c.c. of this mixture in most cases is all that is required. Where, from cystoscopy, a posterior wall diverticulum is suspected, the undiluted 12½ per cent. sodium iodide solution should be used, as this gives a more satisfactory lateral cystogram. Anteroposterior and lateral or oblique views are taken. Some advise stereoscopic X-rays.

After the cystograms have been taken, Swift Joly advises that a rubber catheter should be passed to draw off the iodide from the bladder, and then another X-ray is taken. If iodide is *seen retained in the diverticulum, the amount of it is looked* upon as an index of the stasis in the diverticulum. Swift Joly calls this "concealed residual urine."

Contrast *cystography has been practised, although* I have not used it. After the ordinary cystogram has been taken, the iodide *is withdrawn* using a rubber catheter, no suprapubic pressure being exerted, and 150 c.c. air injected. The contrast cystogram will show up the presence or absence of a non-draining diverticulum, according to *whether any* iodide has been *retained in* the diverticulum or not.

Etiology

There is a cleavage of *opinion among* authorities upon the congenital factor in the production of a diverticulum, but opinion is unanimous about the important part played by the obstructive factor—whether that obstruction be at the bladder neck or in the urethra. The predominance of diverticulum in the male sex, and greatest incidence at the *enlarged prostate age,* emphasises the importance of this. Hinman considers that double or hour-glass bladder, the patent dilated urachus, rudimentary ureteric buds, and vesical hernia are distinct and different, and we will not consider those here.

The two factors *in production of a diverticulum appear to be* —

(1) A weakness in the bladder wall—either congenital or acquired, or both.

(2) A chronic obstruction to the outflow of urine at bladder neck or in urethra.

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of the hip which puzzled two orthopædic surgeons. A carcinoma in a bladder diverticulum involving the obturator nerve was ultimately found to be the cause. These cases would seem to lend some support to Close's idea.

(2) *Chronic Obstruction to the Outflow of Urine at Bladder Neck or in Urethra.*—Rose, of St Louis, divides cases of prostatic obstruction into two classes; firstly, those in which obstruction gains control early in the disease and, secondly, those in which the wall of the bladder (by anatomic compensation) retains its ascendancy over the obstruction. In the second type the obstruction is imperfect and develops slowly, and the wall of the bladder compensates readily on relief of the acute dilatation. It is in this type that diverticula develop.

I have seen no case where a much enlarged prostate has been associated with a diverticulum. In the present series the prostates have all been small, including 4 cases with a middle lobe collar. When the histological picture has been a fibro-adenomatous one, there has been a preponderance of fibrous tissue. In 2 cases malignant change was present in the prostate. In 2 cases there was no enlargement of the prostate, but fibrosis of bladder neck (the condition sometimes called Marion's disease).

Cases of diverticula occur with urethral strictures, and in young boys with congenital valves in posterior urethra. No such cases have occurred in the present series. Four cases in this series volunteered the history of a previous diplococcal infection.

Eisenstaedt and McDougall point out that infection may increase the degree of obstruction and also raise the intracystic pressure.

Mechanism of Development

Hinman states that the first effect of mechanical obstruction below the bladder or at its neck is muscular hypertrophy. This gives the appearance of *trabeculation* cystoscopically, because of herniation of the mucosa between the hypertrophied bundles of the detrusor muscle. The mucosal indentations between trabeculations may grow to form *cellules*. In mild, chronic types of obstruction, as in median bar, some of those cellules, particularly those in the region of the ureteric orifices, may be enlarged mechanically to form *diverticula*. I do not consider this is the whole story, as a diverticulum may be present in the absence of fenestration, or with very mild fenestration, and it is only in relatively few instances that cases with grossly fenestrated bladders develop diverticula.

(1) *Weakness in Bladder Wall.*—This weakness is considered by some to be developmental. The bladder develops in two parts: (*a*) the part between the ureters above and the ejaculatory ducts below is formed by portions of the Wolffian ducts and is fixed, and (*b*) the bladder wall, comprising the detrusor muscle, is derived from the cloaca and is mobile and contractile. The ureters run obliquely through the wall of the bladder to form valvular openings, and longitudinal muscle fibres from the ureteric wall spread medially to the other ureteric orifice as Mercier's bar and forwards to the internal meatus as Bell's muscle, and anchor the ureters. This makes a relatively fixed area in the detrusor muscle which itself is essentially mobile. Hinman says the walls of the bladder in the region of ureteral perforation, " are subjected to more than usual tension, and are bent and pulled back and forth with vesical distension and evacuation, thus tending to aggravate the reticulation." The region above and lateral to the ureteric orifice is the common site for diverticula.

Close of Adelaide draws attention to another developmental factor which predisposes to diverticulum formation. This is traction from without. He points out the importance of the Allantoic sheath of Delbet, that condensation of mesoderm which surrounds the bladder and urachus extends upwards with the urachus, and laterally towards the obliterated umbilical arteries. Frequently in dissections he found a projection of this sheath into the obturator foramen. At first he thought this was a rare condition, but he found it in three of the first five pelves he dissected, and in each of the three a considerable bladder diverticulum was found on the attached side, the apex of the mucosal protrusion being firmly held by such an attachment. He has found such an endofascial attachment to the obturator foramen on several occasions since without any diverticulum. He also found a case of diverticulum at operation with an attachment of fascia to the obturator foramen. He points out that a diverticulum, having once begun, need not continue in a lateral direction, but takes the line of least resistance, which is usually posteriorly. In case No 15 of this series, at operation the diverticulum on right side which was removed was found adherent in front of the internal iliac vessels near the obturator foramen, while, through the smaller diverticulum on the left side, I could feel the obturator vessels and canal, hardly appreciating any tissue between them and my finger. Only to-day a lecturer in the University told me of a case of persistent pain in the region

to go out at both the nozzle and the intake tube. Then slightly obstruct the nozzle, and more fluid will go out at the intake tube. Something like this must happen when there is a diverticulum and some obstruction at the bladder neck.

The presence of a diverticulum must cause a weakening in the detrusor effect. Ogier Ward refers to a case of a patient who had a diverticulum with a considerable stone in it. He was able to micturate until the stone was removed from the pouch by operation, but afterwards had difficulty; the suggestion being that removal of the calculus uncorked the diverticulum. In case No. 17 the larger half of a dumb-bell stone was removed from a diverticulum which it filled The diverticulum was a small and adherent one, and an attempt to remove it had to be given up. The patient passed urine normally on the sixteenth day and apparently had no great weakening of detrusor effect, but this diverticulum was a small adherent one and would probably not distend much.

Complications of a Diverticulum

(1) *Infection.*—This is very liable to occur because of the stagnation of urine within the diverticulum. It may have resulted from the first passing of an instrument. Suprapubic drainage of the bladder is apt to precipitate and aggravate this infection. Infection once established in a bladder with a diverticulum is almost impossible to clear up without removal of the diverticulum. Infection in a diverticulum is apt to spread outside and give peri-diverticulitis.

(2) *Calculus Formation.*—Stagnation and infection predispose to this. In this series there were 4 cases of calculi in diverticula (Cases 1, 2, 17 and 21) One was a dumb-bell calculus that had got broken off. One was a recurrent single calculus, and the other 2 cases had multiple calculi. A cystogram may show the shadow of a calculus outside the bladder area, indicating that the calculus is in a diverticulum (Case 17).

(3) *Tumour Formation*—A considerable number of cases of tumours in diverticula have been reported. There is one—a malignant papilloma—in this series (Case 5). In another case a papilloma was present in the bladder just outside the diverticulum (Case 7).

(4) *Perforation or Rupture.*—Kretschmer in his series of 236 cases did not meet with a case of perforation. In this small series there were two such cases. Perforation has usually resulted

Of 17 cases in this series where a satisfactory view of the bladder musculature was obtained by cystoscopy or at operation, in only 6 instances was there a well-marked generalised fenestration. In the other 11 cases fenestration was absent or minimal, being confined to the area lateral to the ureteric orifices.

Young considers the act of micturition is initiated by the trigonal muscle contracting and pulling back the posterior lip of the bladder neck and internal sphincter. Frontz and Landes analysed the behaviour of the trigonal and detrusor muscles in diseases, mainly of obstructive type, of the bladder neck. They conclude that median bar and small middle lobe formation involving the posterior commissure cause a hypertrophy of the trigonal muscle, whereas hypertrophy of the lateral lobes of the prostate alone does not cause any trigonal hypertrophy. Muschat points out the obstruction in this latter type of case is not due to interference with the trigonal mechanism, but due to the compressed and elongated posterior urethra caused by the enlarged lateral lobes of the prostate. To overcome this type of obstruction it is the detrusor muscle that hypertrophies. Muschat measured the thickness of the trigone and detrusor muscles in various forms of bladder neck obstruction in specimens removed at autopsy, and confirmed the clinical observations of Frontz and Landes. The detrusor muscle may hypertrophy in the later stages of posterior vesical lip pathology when the trigonal hypertrophy fails to compensate and no longer opens the vesical neck

The fact that there was no case of great prostatic enlargement in this series, and that in only 6 cases out of 17 was there well-marked generalised fenestration, suggests that detrusor hypertrophy is not so important a factor in the production of diverticula as trigonal hypertrophy, with its causal median bar, middle lobe formation or prostatic fibrosis

If, after a cystogram has been taken, the patient is asked to empty his bladder, and another X-ray is taken, this second picture shows the bladder to be smaller and the diverticulum larger than in the first X-ray (Fig 1) Thus we see how each contraction of the bladder must distend the diverticulum

To illustrate this pulsion factor in diverticulum production, let us take a Higginson's enema syringe and fill it with water. Let the nozzle represent the urethra and the bulb the bladder. Compression of the bulb empties the water through the nozzle as in the evacuation of a normal bladder. Remove the valve from the intake tube, and pressure of the bulb will cause the fluid

of uræmia, and the other of pyelonephritis) Another case developed a stone in the diverticulum.

Urinary Function in the Presence of a Bladder Diverticulum

Swift Joly pointed out that the presence of concealed residual urine in a diverticulum vitiates all tests of renal efficiency which are carried out on the bladder urine, and that to obtain an accurate estimate of renal function it is necessary either to catheterise the ureters, or to trust to the estimation of blood urea.

In this series the blood urea was estimated in 21 of the cases, and in 14 of them was below 50 mgs. per cent.

I sometimes wonder whether the diverticulum has a "safety valve" action and tends to delay the onset of renal impairment due to the back pressure effect of the bladder neck obstruction.

Effect of a Suprapubic Cystostomy in Presence of a Bladder Diverticulum

Drainage of the bladder in these cases, especially in the presence of infection, causes contracture and some fibrosis in the bladder wall. Its capacity is reduced to between 80-100 c.c., estimated after clamping of the suprapubic tube. This bladder drainage does *not* drain the diverticulum and tends to narrow the opening into the bladder slightly, and the openings of diverticula are still readily recognisable on cystoscopy in the contracted and drained bladder. Stagnation and infection in the diverticulum are increased, as the absence of detrusor effort occasioned by the presence of the suprapubic drain also prevents the periodic distension of the diverticulum when the bladder contracts.

Indications for Removal of a Bladder Diverticulum

(Assuming that the renal function is satisfactory, and that two consecutive blood urea readings are below 50 mgs per cent.)

The criteria by which one would advise removal of the diverticulum are as follows :—

1 *Where the Diverticulum is of the "Retention" Type*—
   This includes all large and medium-sized diverticula. This can be determined by :—

from ulceration caused by intensity of infection. Rupture took place into peritoneal cavity (Cases 1 and 7).

(5) *Adhesion of Diverticulum to Ureter giving Unilateral Hydronephrosis.*—There is one case of this in the present series (Case 16). Kretschmer has pointed out that a large diverticulum may be present for a great many years without any deleterious effect on the upper urinary tract, whereas a small diverticulum in intimate relationship with the ureter may produce a marked hydronephrosis.

(6) *Ureter opening into a Diverticulum.*—No case of this was encountered.

(7) *Tubercle* } occurring in a diverticulum have both been
(8) *Leukoplakia* } reported by various authors.

Life History of Diverticula

There has been an opportunity of watching the after-progress of 6 cases in which the diverticulum was *not* removed In 2 of these cases no treatment was carried out. In 3 cases a suprapubic prostatectomy was done, and in 1 case an endoscopic resection of the prostate was carried out. In Case 3 a small diverticulum was found on investigating the cause of hæmaturia An incidental cystogram was given by iodide regurgitating into the bladder from a pyelogram Ten years later an intravenous pyelogram also gave an incidental cystogram. The diverticulum was now seen to be slightly larger and slightly more globular There was no demonstrable bladder neck obstruction in this case, and no symptoms of it. This illustrates the small change in a diverticulum in the course of ten years without a bladder neck obstruction

In the cases of the three prostatectomies, one developed a stone in his diverticulum two and a half years later, and had no symptoms till a piece broke off Another case died of pyelonephritis eleven months after operation The third lived for six years and died of senility

The patient with the endoscopic resection died ten years later from uræmia—his urine remained infected all the time

The last case in this group, after being diagnosed, was not seen for three years, and then came in in a hurry with a gross infection and died of uræmia, no treatment having been carried out.

Thus in these 6 cases where the diverticulum was not removed, 3 were grossly infected (two of them dying ultimately

Separate drainage of diverticulum to exterior has also been done, either after cutting through communication with bladder where diverticulum is adherent (de Illeyés), or when communication with bladder is not attacked. This latter might have to be done if diverticulum grossly infected.

I. *Removal of Diverticulum.*

A. *Intraperitoneal.*—I have not had to do this. It would be necessary with diverticulum of urachus.

B. *Extraperitoneal Approach.*

(*a*) Extravesical.

(*b*) Intra- or trans-vesical.

(*c*) Combined—the method of my choice.

Pre-operative Treatment.

Attempted control of infection by giving one of the sulphonamides or mandelic acid is not likely to be helpful.

Passage of Ureteric Catheters.—I consider this should be done where the diverticulum is suspected to be adherent, in order to act as a guide to the ureter.

Anæsthetic.—Spinal anæsthesia is ideal, provided the patient is a suitable subject, as relaxation of the abdominal muscles and contraction of the intestines greatly facilitate access to pelvis. The modified Trendelenberg position is used.

Operation.—A catheter is passed and the bladder is filled with sterile water until it is palpable suprapubically.

My preference is for the extravesical approach, with the bladder still distended and unopened, but finish up by the transvesical route to define the neck of the diverticulum accurately.

A median subumbilical incision is made, and the peritoneal reflection is dissected upwards as far as possible without opening the peritoneal cavity. Blunt dissection is carried out lateral to the bladder on the side of the diverticulum. If the diverticulum is posterior, approach can be made from either side. The diverticulum, if non-adherent, can be fairly easily defined all round by blunt dissection, this dissection becoming a little more difficult towards the neck where the diverticulum opens into the bladder. Occasionally a localised adhesion to the side wall or floor of the pelvis may have to be divided before the diverticulum can be brought up into the wound (The presence of an adhesion is indicated in the cystogram by any tendency to pointing in the

(*a*) *The coiled catheter test* where, through the cystoscope, the whole length of a ureteric catheter can be coiled up in the diverticulum. (One might except in this group the wide mouth diverticulum found behind the inter-ureteric bar.)

(*b*) *The concealed residual urine* method of Swift Joly gives an idea of the size and degree of stagnation in the diverticulum. Contrast cystography can also give this information.

2. *If the Diverticulum is complicated by Stone, Tumour, etc.*—The fact that a tumour may lie undetected in a diverticulum emphasises the importance of removal of a diverticulum in cases of hæmaturia, where no cause for the hæmaturia can be found.
3. If there is a unilateral hydronephrosis on the side of the diverticulum, and the suspicion is that the diverticulum is adherent to the ureter.

Removal of diverticulum is not *undertaken*—

1. Where the *coiled catheter test* is negative; where the diverticulum is so shallow or the neck of diverticulum so relatively wide that the point of catheter curves out of, or is arrested in a diverticulum after passing in only a few centimetres.
2. If the patient is seventy years or older (when an endoscopic resection of prostate alone should be done) If the diverticulum is a very large one, removal might have to be risked
3. If diverticula are *multiple* The consensus of published opinion appears to consider multiplicity a contra-indication to removal. Multiple diverticula are apt to be small, but a large diverticulum I feel should be removed, and any accompanying small ones left.

Treatment of bladder diverticulum falls under two headings.—

I. Removal of diverticulum
II. Treatment of bladder neck obstruction.

Operations on the orifice of a diverticulum, e g. stretching or enlargement by cutting the orifice downwards and outwards, are not considered satisfactory, although successful cases are reported by Rowlands and de Illeyés

If the diverticulum is grossly infected it would be wise to syringe or wash out the diverticulum evacuating the fluid with the sucker. Silver nitrate 1 in 10,000 or oxycyanide of mercury 1 in 4000 could be used. An incision is then made through the bladder wall to the orifice of the diverticulum. The incision may be converted into a racquet one, by being continued round the opening of the diverticulum if the ureteric orifice is quite clear, *or* the incision continued through lateral margin of orifice to divide the lower part of the antero-lateral wall of the diverticulum. In this way the lining of the diverticulum and possibly some of its fibro-muscular coat may be removed. The opening in the bladder would be closed by two layers of interrupted catgut stitches.

Other methods of removing the diverticulum which I have not used :—

(*a*) *Tenaculum forceps method of Young*, where a circular incision is made round the orifice of the diverticulum from the bladder. The lining of the diverticulum is caught with forceps, and is dissected free like the Whitehead operation for piles.

(*b*) *Suction method of Young*, where he inverts the diverticulum into the bladder by suction, and then excises it.

Where the ureteric orifice has been drawn just within the diverticulum, Young, instead of making a circular incison round the orifice, makes a crescent moon incision to avoid the orifice, and does a plastic repair.

II. *Treatment of Bladder Neck Obstruction.*

1. Prostatectomy or removal of middle lobe collar.
2. Endoscopic resection with McCarthy resectoscope or cold punch.

1. When possible and advisable the prostate should be enucleated at the same time as the diverticulum is removed.

The prostates associated with bladder diverticula are small and apt to be very fibrotic, and attempted enucleation may meet with no success In some cases there is a middle lobe collar, and removal of this may be all that is required ; this can usually be done although the rest of the prostate is too fibrous to enucleate.

If I am unable to enucleate the prostate, and there is no middle collar to remove, I dilate the prostatic urethra with the finger. This can only be a temporary measure, and should be

outline of the diverticulum which is usually globular, except where flattened by the side wall of the pelvis.)

The *identification of the ureter* can be more easily done before the bladder is opened, but, in the case of a large diverticulum, the bladder and diverticulum may have to be emptied first. A medium-sized diverticulum may strip easily to its neck, and the opening of the diverticulum may be known by cystoscopy to be well clear of the ureteric orifice, so that in such a case identification of the ureter may not be necessary. The ureter is picked up, as it approaches the bladder base, by blunt dissection in the pelvic cellular tissue. This exposure of the ureter is especially necessary in small diverticula nestling close to the bladder base. Once defined, the ureter is held aside by a pair of Fullerton's ring forceps. The vas deferens may be encountered close to the bladder base, as it passes from lateral to medial side in front of the ureter.

The bladder is opened in the mid-line by a vertical incision, and the fluid evacuated with the sucker. The diverticulum is explored with the finger to exclude any tumour. If further dissection has to be done to define the neck, either the finger or a ribbon gauze are put in the diverticulum. For the final definition of the neck, the fundus of the diverticulum may be grasped by a pair of Lane's forceps, and the neck exposed by dissecting with a pair of curved-on-the-flat Mayo's scissors.

Should a tumour be suspected in the diverticulum, it would probably be advisable to open the bladder earlier, before handling and defining the diverticulum, lest the tumour break off into the bladder. The diverticulum could be defined after it had been shut up by a ribbon gauze pack

The neck is cut out of the bladder wall; if the bladder wall is thinned round the orifice of the diverticulum an ellipse of bladder wall can be taken out along with the diverticulum Two layers of interrupted catgut sutures are put in to close the opening in the bladder, in such a way that no catgut or raw area presents to the interior of the bladder to favour incrustation

A rubber dam drain (or a gauze pack soaked in sterile liquid paraffin) is put down to the bed of the diverticulum outside the bladder, and brought out through the lower part of the wound. This drain is left in for four to six days The bladder is drained by a small Freyer's tube or a Malecot tube size 28 or 30.

In the case of a diverticulum suspected to be *adherent* the bladder is opened before attempting to define the diverticulum.

If the diverticulum is grossly infected it would be wise to syringe or wash out the diverticulum evacuating the fluid with the sucker. Silver nitrate 1 in 10,000 or oxycyanide of mercury 1 in 4000 could be used. An incision is then made through the bladder wall to the orifice of the diverticulum. The incision may be converted into a racquet one, by being continued round the opening of the diverticulum if the ureteric orifice is quite clear, *or* the incision continued through lateral margin of orifice to divide the lower part of the antero-lateral wall of the diverticulum. In this way the lining of the diverticulum and possibly some of its fibro-muscular coat may be removed. The opening in the bladder would be closed by two layers of interrupted catgut stitches

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followed by an endoscopic resection. It might be possible in these cases to widen the bladder neck by the original Young's prostatic punch, done under direct vision, or by the clamp incisor described by W. K. Irwin.

2. *Endoscopic Resection of Bladder Neck.*—I used the McCarthy resectoscope to enlarge the bladder neck in 4 cases in this series. Among urologists who do many endoscopic resections of the prostate, I understand that the cold punch (Braasch-Bumpus or Gershom Thompson instrument) is preferred.

In 1940 Gershom Thompson, Kermott and Cabot reported a series of 96 cases of diverticulum from the Mayo Clinic treated by transurethral resection alone without diverticulectomy. They state that in recent years diverticulectomy has been infrequently done in the Mayo Clinic, and rarely in patients of advanced years. They consider that diverticulectomy, however, is indicated in certain definite types of case: (1) Where diverticulum is of medium or large size, with a very small, tight orifice through which drainage is unsatisfactory. (2) In relatively young men having a fair-sized diverticula, even though there are no definite symptoms, but in whom the diverticula do not drain well after transurethral resection of the prostate. (3) Where there are complicating factors such as stone and carcinoma. (4) Where ureteral obstruction and hydronephrosis are caused by an adjacent diverticulum. At least 7 of the 9 cases in this series in which a diverticulum was removed appear to have fulfilled these indications.

The Order of Procedure is of Considerable Importance in the Treatment of a Diverticulum.—The ideal is removal of the diverticulum and the prostate at one stage.

Removal of the prostate first is not satisfactory on account of sepsis—2 out of 3 cases in this series were unsatisfactory. Thompson, Kermott and Cabot, in reviewing 14 cases of diverticulum of bladder who were treated only by prostatectomy, found the post-operative convalescence was eventful, and several patients suffered from epididymitis and cystitis. Ogier Ward did an endoscopic resection of prostate without removal of diverticulum in 4 of his series of 53 cases, and all were unsuccessful—sepsis being the trouble

Thompson, Kermott and Cabot state that in their series the immediate post-operative course of each patient was smooth, and similar to any other patient treated by transurethral resection. They state categorically that, " Transurethral resection in contrast

with suprapubic prostatectomy in no wise increases the difficulty or danger of subsequent diverculectomy."

Removal of the diverticulum first is not open to the same objections. The prostate can be dealt with later by second stage suprapubic removal or endoscopic resection.

In cases where a suprapubic cystostomy has had to be done for acute retention, or for chronic retention where it has not been possible to pass a cystoscope, the diagnosis of diverticulum has not been made. The subsequent removal of the diverticulum becomes more difficult.

Finally, I would emphasise again that these cases are everyday, ordinary cases coming to the general surgeon, and that the early recognition of the presence of a diverticulum holds out the best prospect for both patient and surgeon.

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OBSERVATIONS ON ECLAMPTIC TOXÆMIA AND ON ESSENTIAL HYPERTENSION AND CHRONIC NEPHRITIS IN PREGNANCY

By DOUGLAS MILLER, M.D., F.R.C.S.Ed., F.R.C.P.Ed., F.R.C.O.G.

RECENT advances in our knowledge of hypertensive cardiovascular disease and of nephritis make it desirable to bring under review the contribution made thereby towards a clearer understanding of the nature of eclamptic toxæmia and its relationship to the other hypertensive disorders of pregnancy. Until comparatively recently it has been customary to regard eclampsia as a disorder in which the liver and, to a less extent, the kidneys and central nervous system are disorganised in consequence of the action of a hypothetical toxin of unknown nature and origin. In 1924, however, Volhard [1] advanced the view that eclamptic toxæmia was a manifestation of a generalised spasmodic vaso-constriction of the smaller arterioles and capillaries, and claimed that all the clinical and pathological findings could be explained on this basis. Volhard's work was of fundamental importance, and it may be said at once that his observations have since been substantially confirmed and amplified by the observations of numerous writers [2, 3, 4] both in Germany and America, and to a less extent in this country. These studies have shown convincingly that all the pathological changes of pre-eclampsia and eclampsia as well as its clinical features can be interpreted satisfactorily on the basis of a generalised vascular spasm. It is of interest that as early as 1914 James Young,[5] though he did not appreciate the generalised nature of the circulatory disturbance, insisted that the changes in the uterine wall and placenta were essentially vascular in character.

It is necessary to review shortly the evidence on which this modern conception of eclamptic toxæmia is based. In the first place, the most constant and characteristic as well as in most cases the earliest disturbance of pre-eclampsia is a rise of blood pressure, attributable to the increased peripheral resistance caused by the general arterial spasm As in early hypertension apart from pregnancy,[6] it is noteworthy that in patients who

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subsequently develop toxæmia the systolic blood-pressure level is found to be variable and unstable, being abnormally sensitive to emotional or other stimuli. It is, for example, a common experience to find in such cases that the systolic pressure reading may drop by 20 points after the patient has rested quietly for a quarter of an hour in the consulting room or within a day or two after admission to hospital with no treatment other than rest. In any pregnant woman such instability in the blood-pressure is to be regarded as indicating a proclivity to toxæmia, and Browne,[7] in particular, has drawn attention to the significance of this transient "warning rise."

Another indication of the abnormally labile nature of the blood-pressure of the potential pre-eclamptic is illustrated by its reaction to the cold-pressor test of Hines and Brown.[8] This test consists in recording the effect on the blood-pressure of immersion of the hand in ice-cold water for sixty seconds. It has been employed by Dieckmann,[9] Browne[10] and others in the antenatal clinic in an effort to identify women likely to develop pre-eclampsia. Dieckmann found that out of ninety patients with a positive response, toxæmia subsequently appeared in 25 per cent., whereas out of sixty-two patients with a negative response only 3 per cent. developed toxæmia. Browne's results were broadly similar and he considered that the test had a practical value.

Further evidence pointing in the same direction is the familial tendency to hypertension noted in the case histories of a significant proportion of toxic patients. Herrick,[11] who was one of the first to make this observation, believes that in such women, had pregnancy not occurred, hypertensive changes would have appeared in middle life; pregnancy, however, has a potent influence in bringing to the surface a latent tendency to hypertension or in aggravating it if already present.

The existence of a widespread angio-spasm in toxæmia, which may be inferred from these observations, is capable of more direct demonstration by examination of the eye-grounds, in which spasmodic contraction of the retinal blood vessels is a common feature,[12] and by the detection by the capillary microscope of similar changes in the capillaries at the base of the finger nails. A generalised vaso-constriction of this kind appears to offer a satisfying explanation of the sequence in which the symptoms of toxæmia appear and of their nature, and is also in accord with the finding that where after-effects persist the residual lesion is essentially vascular in character.

The Relationship of Eclamptic Toxæmia to Essential Hypertension

Pre-eclampsia and essential hypertension have as their common basis a generalised arterial spasm, and are so closely similar in their clinical and pathological features that many writers have sought to identify the one disease with the other. So authoritative an observer as Fishberg,[13] for example, states "that the *hypertension of toxæmia is classical essential* hypertension, not to be differentiated by any clinical or anatomical criterion of which I am aware from essential hypertension in the male." Granted that the resemblance is a close one, there still seem adequate grounds for considering eclamptic toxæmia as an entity in itself. The fact that in an individual, with or without a predisposition to hypertension, pregnancy supplies the stimulus, whatever its nature may be, which results in the syndrome of symptoms which we term toxæmia, suggests that the latter should be regarded as a disorder specifically dependent on pregnancy. Moreover, the clinical course of toxæmia, occurring as it does with rare exceptions only in the latter half of pregnancy, reaching its climax and rapidly subsiding post-partum, and in fully 60 per cent. of cases leaving no sequelæ of any kind, is in favour of this view. While, therefore, these two conditions are basically similar, it seems wise to continue as heretofore to regard eclampsia as an entity in itself, peculiar to pregnancy.

The Relationship of Chronic Nephritis to Eclamptic Toxæmia

Chronic Nephritis.—The common finding of albumen in the urine in toxæmia has in the past resulted in impairment of kidney function being regarded wrongly as an important factor in pathogenesis and also as a primary consideration in treatment. This misconception is reflected in the use of such terms as "nephritis of pregnancy," "nephritic toxæmia," "occult nephritis" and "low reserve kidney," all of which are unfortunate in that they place undue emphasis on the rôle which the kidney plays, and tend to obscure the fact that in toxæmia the disturbance is primarily a generalised vascular lesion, impairment of the kidney being either entirely absent or occurring only as an incidental or secondary effect. The same objection applies to the view

commonly expressed that "pregnancy throws a great strain on the kidneys." There is no evidence whatsoever that in a pregnant woman in normal health the kidneys are in any way embarrassed by the increased demands of pregnancy. Numerous cases are on record of one kidney being removed before or during pregnancy with no indication of the slightest impairment of function in the other organ. Even in pre-eclampsia the standard tests of renal function do not in the majority of cases show appreciable deviation from normal, provided that the kidney function was adequate prior to pregnancy.

There is therefore no evidence either that pre-eclamptic toxæmia is a manifestation of impaired kidney function, or that a pre-existing chronic nephritis is ever to be regarded as in itself a cause of toxæmia The two conditions are totally distinct the one from the other. On the other hand, whether or not chronic glomerulo-nephritis predisposes to the development of toxæmia is a more open question. There are arguments, which time does not permit me to advance, in favour of the view that it does so.

Pyelo-nephritis.—It is generally believed that no direct relationship exists between acute pyelo-nephritis and pre-eclampsia. On the other hand, Peters [14] in a recent investigation of 320 toxic patients, found that 13 per cent. suffered at the same time from pyelitis or pyelo-nephritis, and from the examination of clinical and post-mortem material considered that these conditions were etiologically related. The Edinburgh Maternity Hospital records show that in any one pregnancy it is exceptional for pyelitis to be followed by toxæmia. On the other hand, the studies of Dexter and Weiss,[15] of Peters,[14] and of Crabtree and Reid [16] have emphasised that pyelitis of pregnancy is seldom the transitory disturbance which it has been regarded in the past by the majority of obstetricians. Follow-up urological investigation has shown that the disappearance of symptoms and a chemically clear urine do not necessarily indicate complete recovery, and that in a considerable proportion of patients the lesion is a progressive one resulting after an interval of some years in appreciable impairment of kidney function and in renal hypertension While, therefore, there is no evidence that acute pyelitis is ever an immediate or even a predisposing cause of toxæmia in the same pregnancy, it may increase the liability to the occurrence of toxæmia in subsequent pregnancies through the agency of renal damage and hypertension.

Classification and Differential Diagnosis

The lack of a generally accepted classification of eclamptic toxæmia and similar disorders complicating pregnancy, the failure to distinguish clearly between these various entities, and the employment of a loose and frequently misleading terminology, have combined to delay a clear understanding of their nature and relationships.

Of the numerous classifications which have been suggested, that offered by Goldring[17] has the merits of being simple, sufficiently comprehensive, and in accord with modern clinical and pathological knowledge. Slightly modified it is as follows: (1) specific toxæmia of pregnancy with or without convulsions, *i.e.* pre-eclampsia or eclampsia; (2) pregnancy complicated by pre-existing essential hypertension; (3) pregnancy complicated by chronic or acute glomerulo-nephritis, by pyelo-nephritis or by nephrosis; (4) toxæmia superimposed on groups 2 and 3. Such a classification might with obvious advantages be employed by our larger maternity hospitals and incorporated in their annual reports.

The difficulties of accurate differentiation are, it must be admitted, considerable and not infrequently insuperable. It may be impossible, for example, to place in its proper category a case that is admitted to hospital with severe hypertension and albuminuria, from whom a reliable past history cannot be obtained and who, for one reason or another, is not seen again after the lying-in period is completed. Accurate differentiation into the four groups in the suggested classification may require (1) an accurate knowledge of the patient's health prior to conception or in the early months of pregnancy, (2) observation over a period of months or possibly years subsequent to delivery, or (3) autopsy findings

(1) *Toxæmia of pregnancy* arising *de novo* has as its principal distinguishing features (*a*) a rise in blood-pressure in the later months of pregnancy to a level exceeding 140 systolic and 90 diastolic mm. Hg., accompanied or followed by the appearance of albuminuria and œdema and the other recognised manifestations of pre-eclampsia; (*b*) a partial or complete disappearance of these phenomena after delivery; (*c*) absence of significant impairment of kidney function as shown by standard tests.

(2) *Pre-existing hypertension* can, of course, only be diagnosed with certainty as such if the blood-pressure is known to have been elevated before conception or in the early months of preg-

nancy. The condition may be quite uninfluenced by pregnancy, in which case the symptoms are simply those of hypertensive cardio-vascular disease *per se*, and the fact that they show no progressive tendency during pregnancy and no diminution after delivery serves to distinguish it from toxæmia. Alternatively, pregnancy may be associated with an aggravation in symptoms which are indistinguishable from pre-eclampsia and which should probably be regarded as a superimposed toxæmia

(3) *Glomerulo-nephritis.*—(*a*) Acute glomerulo-nephritis is an exceptionally rare complication of pregnancy, only four cases having been diagnosed as such during the past fifteen years in the Edinburgh Royal Maternity Hospital. This figure may not accurately represent its incidence, for the resemblance between acute nephritis and severe pre-eclampsia is so close that they may readily be mistaken the one for the other, and it is possible that errors in diagnosis have been made. Although the structural changes in the kidney are different in the two diseases, all the symptoms and signs in the one may parallel those in the other so closely, with the exception of the character of the urinary sediment, that the difficulty of clinical differentiation may be insuperable and a correct diagnosis only possible in the follow-up clinic or on the post-mortem table.

(*b*) Chronic glomerulo-nephritis is not a common complication of pregnancy. During the past fifteen years, eighty-nine cases diagnosed as "chronic nephritis" appear in our hospital records, an incidence of approximately three per one thousand patients delivered. This figure undoubtedly overstates the frequency of the complication owing to selective hospitalisation and the erroneous grouping of all the chronic nephropathies under the label "chronic nephritis."

The diagnosis of chronic glomerulo-nephritis complicating pregnancy may be simple if the patient is known to have displayed its characteristic features before conception or in the first half of pregnancy. On the other hand, if the patient is not seen till the later weeks of pregnancy and a reliable history of her previous health is not obtainable, it may be difficult to distinguish it from toxæmia. An unequivocal past history of acute nephritis supports a diagnosis of chronic nephritis, but it must not be forgotten (1) that a patient may make a complete recovery from an acute nephritis and develop eclamptic toxæmia in a subsequent pregnancy, and (2) that occasionally a patient with chronic Bright's disease may have no subjective symptoms, attention

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frequency with which "chronic nephritis" follows eclampsia has been responsible for the most widely divergent figures. Harris,[19] for example, found that in fifty-five patients with pre-eclampsia the incidence of chronic nephritis at the end of one year was as high as 60 per cent. Gibberd[20] found the incidence of chronic nephritis following toxæmia to be 14 per cent.; while in Browne's[10] series of 144 patients chronic glomerulonephritis was not found subsequently in a single case.

Against these conflicting reports may be placed evidence of an unassailable character provided by Theobald,[21] who in 1933 quoted figures from the Registrar-General's decennial report for England and Wales for the years 1911 to 1920, which showed that during this decade there was no significant difference in the death-rate from chronic nephritis between men and women and no difference in this respect between married and single women up to the age of fifty-five. Theobald's conclusion that eclamptic toxæmia could not be a cause of chronic nephritis is in line with Browne's clinical findings that chronic nephritis is not a sequel of toxæmia, and has been amply confirmed by numerous subsequent reports. These later publications are uniformly in accord with the modern conception of the toxæmia of pregnancy as a generalised vascular disturbance, and show clearly that in cases in which after-effects persist, *the residual lesion is essentially one of hypertensive cardio-vascular disease and not chronic nephritis.* It is true that in this circulatory disorder the kidneys may not be unaffected, but statistics show that in not more than 8 per cent. of cases of essential hypertension does renal involvement cause death from uræmia, the common causes of death being cardiac dilatation and cerebral hæmorrhage.

Just as formerly undue emphasis has been placed on the rôle which the kidney plays in the pathogenesis and production of symptoms in toxæmia, so until recently follow-up studies have erroneously directed attention to the kidney as the organ which exhibits such after-effects as may persist This is illustrated by the frequency with which among the dangers of toxæmia is instanced that of "permanent damage to the kidneys," an expression which is misleading. It is reflected also in the prominence given to the mistaken interpretation of recurrent toxæmia as being due to a "low reserve kidney," or to an "occult" or "concealed" nephritis as suggested respectively by Kellog[22] and by Gibberd.[23] This view, that toxæmia might cause such damage to the kidneys as would not adversely influence

being directed to its presence by the accidental finding of albumen in the urine and the discovery of structural cardio-vascular changes in the course of routine antenatal examination. In general terms, chronic glomerulo-nephritis complicating pregnancy has as its distinctive features (1) the development of such symptoms as lassitude, headache, œdema, anæmia and visual disturbances at an earlier stage in pregnancy than the symptoms of toxæmia generally appear; (2) relatively high blood-pressure readings compared to those found in toxæmia; (3) the presence of structural cardio-vascular changes, as indicated especially by sclerotic radial and retinal arteries and cardiac enlargement, and (4) more pronounced impairment of kidney function than in toxæmia.

(4) *Toxæmia superimposed on pre-existing essential hypertension or on chronic glomerulo-nephritis* may scarcely be diagnosed with accuracy as such without reliable information regarding the patient's previous state of health or without the opportunity of follow-up study. Even if such information is available, the spontaneous fluctuations in the blood-pressure level and other symptoms which characterise both essential hypertension and chronic nephritis may readily be a source of confusion. In general, if in the later weeks of pregnancy there is an appreciable elevation of the blood-pressure level and an aggravation of the other symptoms with a corresponding improvement post-partum, a tentative diagnosis of superimposed toxæmia may be made; but unless prolonged follow-up or autopsy findings are available, the diagnosis is as a rule presumptive rather than positive.

Prognosis

Since Shroeder[18] in 1878 first drew attention to the frequency of renal lesions after eclampsia, much study has been devoted to the incidence and nature of the late sequelæ of eclamptic toxæmia. The widely different findings in regard to both the frequency and the nature of these after-effects has been perhaps the most striking feature of these publications. An analysis of the reports suggests that discrepancies may have arisen from failure to identify accurately the nature of the antecedent disturbance of pregnancy, from inability to determine or exclude the presence of pre-existing essential hypertension and chronic nephritis, and from the use of inexact terminology especially in regard to the nature of the subsequent kidney lesion. The

of hypertensive encephalopathy due to essential hypertension and not true eclampsia.

(2) *Remote Prognosis.*—Reference has already been made to the nature of the after-effects of eclamptic toxæmia and emphasis laid on the fact that these are cardio-vascular rather than renal in character. It is important also to emphasise the essentially progressive nature of the underlying vascular lesion, a consideration of great practical importance in relation to both prognosis and treatment. In this connection it is necessary to refer briefly to the classic experiments of Goldblatt,[29] which have not only made an important direct contribution to our knowledge of hypertension but have stimulated work by others on the source and extraction of pressor and depressor substances, which may prove to be of the greatest practical value in the treatment of toxæmia. It will be recalled that Goldblatt was able to produce hypertension by partial occlusion of one or both renal arteries, the rise in blood-pressure being due to absorption of a pressor substance formed in the ischæmic kidney and being unaccompanied by any disturbance of renal function as indicated by the standard tests. If the renal circulation were restored after a short interval or if the ischæmic kidney were removed, the blood-pressure quickly returned to normal, otherwise a permanent elevation of blood-pressure was established, together with the development of sclerotic changes in the arterioles similar to those found in the human hypertension.

These observations, which have been amply confirmed, appear to throw light on the progressive character of the circulatory disturbance in toxæmia, and suggest that the initial vaso-constriction, which involves the renal as well as the other arterioles, may result in an ischæmia of the kidney with liberation of a pressor substance which further accentuates hypertension and reacts afresh on the kidneys. A vicious circle is thus established which, if it continues long enough, must result in permanent cardio-vascular disease. This conception is in line with the generally accepted view that in eclampsia the incidence of permanent after-effects depends on the duration rather than on the intensity of the preceding toxæmia In other words, the prolonged vaso-constriction of a pre-eclampsia which continues for several weeks is more likely to be followed by permanent arterial damage than the abrupt vaso-spasm of a fulminating eclampsia.

The frequency with which hypertensive disease follows toxæmia

health in the absence of pregnancy, but which would manifest itself when the strain of further pregnancy was added, was opposed in the first place by Young,[24] who disagreed that the tendency to recurrence in toxæmia was due to a residual renal defect. Young's contention has been fully endorsed by other observers, notably by Herrick and Tillmann [25] and by Dieckmann and Brown,[26] the majority of whom are of the opinion that recurrent toxæmia is to be regarded as an expression of latent hypertension which is temporarily aggravated by pregnancy.

Prognosis in Toxæmia Uncomplicated by Pre-existing Hypertension and Chronic Glomerulo-nephritis

(1) *Immediate Prognosis.*—The immediate prognosis in eclampsia received particular attention in the clinical analysis made by Eden [27] in 1921, and although advances in our knowledge have made it necessary to modify certain of the conclusions formed, time has proved these to have been substantially correct. In particular, Eden's grouping of cases into two principal categories according to the severity of symptoms has made it possible to forecast the immediate outcome with reasonable accuracy. It will be recalled that in cases in which two of the following six symptoms occurred—deep coma, more than ten fits, pulse over 120, temperature over 103, systolic blood-pressure over 200, and urine solid with albumen on boiling, the mortality amounted to approximately 32 per cent.; whereas if none of these symptoms was present the mortality did not exceed 7 per cent Possibly of greater importance than any of the six symptoms cited as an index of prognosis, is the occurrence of a drop in blood-pressure, sudden or insidious, which is unaccompanied by other signs of improvement This finding is generally an indication of myocardial failure or peripheral circulatory collapse and is of grave import.

One symptom, the severity of which was found in Eden's series to bear little apparent relation to prognosis was œdema. Indeed, in those cases in whom œdema was slight or absent the outlook was particularly grave This may be explained by the fact that in eclampsia œdema of the brain is not necessarily a mere part of a generalised anasarca, and that it may cause a rise in intracranial tension to a point inconsistent with life, with little or no evidence of œdema elsewhere Alternatively, it is possible that some of these cases of " dry eclampsia " may be examples

cause an aggravation of the disease. Moreover, the permanently harmful effect of pregnancy is reflected in the fact that in approximately one case in three the aggravation due to pregnancy does not subside after delivery.

Prognosis in Chronic Glomerulo-nephritis complicating Pregnancy

While it is true that in exceptional cases the additional burden of pregnancy is well borne by the chronic nephritic, there is as a rule a progressive deterioration in her condition as pregnancy advances. Information supplied by renal function tests, in particular the blood urea, urea concentration and urea clearance tests, and also the fact that in most cases the adverse effect of pregnancy manifests itself much earlier than pre-eclampsia generally appears, suggest that the deterioration in health is due mainly to a further impairment of kidney function rather than to a superimposed toxæmia. Such objective signs as progressive hypertension and albuminuria, œdema becoming more pronounced, increasing nitrogen retention in the blood and structural changes in the retina are of great importance and demand prompt termination of the pregnancy. Even in their absence the prognosis must be guarded, for at any time signs of renal failure may appear, and the pregnancy should be allowed to continue only after the risks both to herself and to the child have been explained to and accepted by the patient. The fœtal and neonatal mortality is very high in this complication, and when account is taken of abortion, both spontaneous and induced, still-births and deaths from prematurity, the expectation of a living child which one can offer before or at the commencement of pregnancy does not exceed one in three

Termination of the pregnancy, though it does not always arrest the downward progress of the disease, is generally at least temporarily beneficial in its effect. The improvement which follows may or may not be maintained, but as a rule with each successive pregnancy the aggravation in symptoms appears earlier and is more severe than before.

Tests of Kidney Function in Relation to Prognosis.—Studies of renal function have on the whole disappointed earlier expectations that they might prove to be as useful in gauging the prognosis of pre-eclampsia as they are in chronic nephritis Bearing in mind that impairment of kidney function is not a primary

has been variously assessed by different writers, the figures ranging from 25 to 50 per cent. In clinics where the admission of patients is restricted to their own ante-natal service, the incidence of permanent damage will naturally be lower than in those like the Edinburgh Maternity Hospital where there is no such selection, and where in many cases there is a long history of untreated pre-eclampsia before admission. Again, in clinics in which, without consideration for the child, it is the usual practice to terminate pregnancy at an early stage of the toxæmia in the interests of the mother, the late prognosis is naturally better than in those where interference is delayed in the hope of delivering an infant with a better chance of survival Where pre-eclampsia or eclampsia develops in a woman previously healthy there is general agreement that in *at least one case in four permanent cardio-vascular damage will be sustained*; it is also the general experience that the incidence of subsequent invalidism depends rather on the duration than on the severity of the antecedent toxæmia.

Prognosis in Pre-existing Essential Hypertension complicating Pregnancy

The frequency with which pre-existing hypertension is adversely influenced by pregnancy is difficult to assess, widely different figures being presented by different writers. Browne[10] using as a standard of hypertension a blood-pressure level of 135 systolic and 70 diastolic, found that in fifty-two out of sixty-five cases there was no appreciable deterioration during pregnancy; in other words, that only 20 per cent. were harmfully affected. These figures seem to invite the criticism that the standard of hypertension is so low that cases may have been included which were not in fact hypertensive, a criticism which receives support from the much higher incidence of aggravation due to pregnancy noted by others. Reid and Teel,[29] for example, after a careful study of 122 patients known to have had hypertension prior to pregnancy, found that in approximately 60 per cent. there was an increase in albuminuria and in the blood-pressure level during pregnancy, and Dexter and Weiss,[30] using as a standard of hypertension the blood-pressure level of 140/90 mm Hg., noted a similar adverse effect in 50 per cent of their cases It appears probable, therefore, that in approximately one-half of patients who are hypertensive before conception, pregnancy will

pre-existing essential hypertension pregnancy will cause an aggravation of symptoms in approximately one case in two, and in one-third of these the deterioration in health due to pregnancy will persist after delivery. (3) In chronic glomerulo-nephritis the influence of pregnancy is almost invariably adverse in both its immediate and remote effects, and the total fœtal and neonatal mortality exceeds 60 per cent. In each successive pregnancy the symptoms tend to appear earlier and are more severe in character. (4) In all these disorders it is frequently impossible to form a final prognosis until several weeks or even months have elapsed after delivery. In many cases symptoms disappear gradually, while in others and possibly more frequently, there is a temporary improvement, even to the extent of complete clinical recovery post-partum, which, however, is not maintained. (5) Tests of renal function are of restricted value in both the early and the remote prognosis of toxæmia or of hypertension, but they are useful in differentiating these conditions from chronic nephritis, In chronic nephritis, taken along with the clinical manifestations. a series of reading provides a useful guide as to the extent to which kidney function is depressed.

Treatment

Within the past two decades three fundamental changes have occurred in the treatment of eclamptic or potentially eclamptic patients which have had a profound influence on the incidence, general course, and after-effects of the disease. The first of these is the recognition of the opportunity which routine antenatal examination affords of detecting its earliest manifestations and of instituting treatment which, even if it is not curative, yet can in most cases prevent the onset of convulsions. The second is the replacement of radical by conservative and more rational methods of treatment in eclampsia, with which the names of Stroganoff and of Tweedie of Dublin must always be honourably associated. The third is the recognition of the importance of follow-up studies and the value of after-care in preventing or minimising subsequent invalidism. Identification of the potentially toxic patient by evidence of inheritance or of emotional or bodily habitus, and detection of incipient pre-eclampsia by the results of periodic examinations of the blood-pressure and urine, or abnormal gain in weight, offer the best hope of early and effective treatment.

cause of toxæmia but a secondary and often late effect, it is not surprising to find that in the great majority of cases of pre-eclampsia tests of renal function give values well within normal limits. *On this point our observations in the Royal Maternity Hospital* are in close accord with those of others and indicate clearly that it is only in the late and more severe stages of toxæmia, and by no means always then, that significant impairment of renal function can be demonstrated. This generalisation applies also to cases of essential hypertension complicating pregnancy in which, as is the case apart from pregnancy, an appreciable degree of renal failure is exceptional unless as an occasional terminal phenomenon.

In cases of severe toxæmia associated with the depressed renal function efficiency tests generally regain their normal value by the end of the second week post-partum. Harris,[31] however, on the basis of a large series of observations, has pointed out that these negative findings at the end of the lying-in period may be misleading, for after the rest and supervision enjoyed in the hospital is replaced by home conditions, evidence of impaired renal function may reappear, and tests carried out six months after delivery may give less normal values than those made a fortnight post-partum. *Incidentally, this observation applies with* equal force to blood-pressure readings and other indications of post-toxæmic invalidism.

In chronic glomerulo-nephritis complicating pregnancy, renal function tests are of relatively greater value. It is necessary, however, to remember the effect of extrarenal influences such as severe anæmia or cardiac decompensation, and that the results of the repeated tests, showing, for example, a progressive impairment of function or progressive recovery, are of greater value *than that of a single reading* These fallacies and limitations make it advisable to accept with reserve the information which renal function tests supply and to interpret them along with the clinical findings.

There is sufficient statistical evidence to warrant the following general conclusions in regard to prognosis : (*1*) *In pre-eclamptic* and eclamptic toxæmia, uncomplicated by antecedent hypertension or chronic nephritis, residual vascular lesions will be found in approximately one case in four. Their occurrence depends on the duration rather than on the intensity of the toxæmia. In a smaller proportion of cases recovery is clinically perfect, but the tendency to toxæmia will reveal itself in subsequent pregnancies. (2) In

and that the prevention of renal failure was a first principle in treatment. Fluids were forced, protein intake drastically reduced, and not infrequently saline infusions were administered. Since, at this stage at least, there is no evidence of renal failure such a regime is unnecessary and, even if renal function were impaired, it is out of keeping with what is now known of the pathology of œdema and of the harmful effect of sodium salts. Where there is evidence of water retention and oliguria, the forcing of fluids aggravates the tendency to œdema and increases intracranial tension without an accompanying increase in the urinary output. *Severe restriction of the fluid intake* to a point where it does not exceed the output is therefore desirable, except in cases in which the concentrating power of the kidney is seriously impaired.

Again, although the exact mechanism of œdema in pregnancy is obscure, there is general agreement that depression of the plasma protein by restriction of the protein in the diet may be an important aggravating factor. In the majority of cases, even in severe pre-eclampsia, provided there is not the complication of a previous nephritis, the concentrating power of the kidney is not diminished and nitrogen retention is not more than slight There is therefore nothing to be gained by employing a low protein diet. *An adequate intake of protein* amounting to 100 grams daily is rational, and is specially desirable when much protein is being lost in the form of albumen in the urine.

The third desideratum in the diet is that it should be *salt-poor in the milder types of toxæmia and as salt-free as possible when symptoms are severe.* Retention of salt in the tissues is an important factor in œdema, and it has been clearly demonstrated that the degree of œdema, and to a less extent the blood-pressure level and the amount of albuminuria, are influenced adversely or beneficially by increase or decrease in the salt content of the diet.[34, 35] As it is the sodium ion which is harmful, such drugs as sodium bicarbonate should not be employed in the treatment of heartburn in toxic patients, nor should this drug be used in gastric or colonic lavage

Treatment by "Elimination."—Another respect in which the management of severe pre-eclampsia which was formerly in vogue has been replaced by a more rational therapy, is the abandonment of forced catharsis, diuresis, and diaphoresis in an attempt to eliminate a hypothetical toxin. With the reservation that the loss of fluid achieved by the reasonable use of magnesium sulphate is beneficial, it is doubtful whether the weakening and

Bearing in mind that œdema is one of the earliest and most significant signs of toxæmia and that it may be present without obvious objective signs, monthly weighing is of great practical value and should be a routine item in ante-natal examination *In the detection of incipient toxæmia determination of the blood-pressure level and of changes in weight are of greater importance than examination of the urine for albumen, for albuminuria may not appear until the toxic disturbance has been established for some time.* This is a point on which strong emphasis must be laid, for although in cases admitted to hospital routine urine examinations have seldom been omitted, it is not unusual to find that periodic examination of the blood-pressure has not been made or, if it has, that a rise in pressure has been discounted as of little or of no significance unless accompanied by albuminuria. The danger of this attitude is illustrated by the fact that several cases have been described, two of them by Theobald,[32] in which eclampsia itself has been unaccompanied by albuminuria. Mudaliar,[33] also, has recorded a series of forty-eight cases of eclampsia, in six of which not more than a trace of albumen was present at any time, while in four others this symptom was absent until after the onset of convulsions

The question may be asked whether in a patient whose past history or present condition makes it probable that toxæmia will appear there is any treatment or regime that will reduce the likelihood of this development. The answer is unfortunately in the negative. Beyond the usual advice normally given to the healthy parturient woman in regard to diet and her conduct of life generally, there are no specific measures which can be relied on to diminish the risk of its occurrence. In particular, for reasons that will be given later, the advice often given to restrict proteins and increase fluids, to "flush out the kidneys" is not only quite ineffective in the direction desired, but may prove actively harmful.

Treatment of Pre-eclampsia. (1) *Rest.*—Complete physical and mental rest, such as can be secured more effectively in hospital than at home, is of the first importance. Every obstetrician has been impressed by the improvement in hypertension and other symptoms which generally follows the institution of rest and a regular hospital regime without any other treatment

(2) *Diet.*—In the past, dietetic considerations have been dominated by the erroneous conception that depressed renal function played an important part in the production of symptoms,

some the effects were strikingly beneficial. While final judgment on these claims must be suspended, their confirmation would imply that a therapeutic agent of the greatest value has been discovered, and we may reasonably cherish the hope that its beneficial effects in non-pregnant hypertension may also be obtained in the closely parallel hypertensive toxæmia of pregnancy.

Termination of Pregnancy.—The obstetrician is seldom confronted by a problem in which greater experience and discrimination are required than that of deciding when and by what means pregnancy should be terminated in the conditions under review. In all cases the decision must necessarily be governed by three important general considerations: (1) the essentially progressive nature of the disease, despite spontaneous fluctuations and temporary improvement with treatment; (2) the ever-present possibility of a sudden, unpredictable exacerbation, with the development of convulsions; and (3) the fact that permanent vascular damage depends on the duration rather than on the intensity of the toxæmia.

In general terms, it may be stated that with few exceptions pregnancy should be interrupted as soon as there is a reasonable chance that the child is sufficiently mature to survive. The view that the interests of the mother and child are in conflict is only a half truth, for in most cases a stage is reached when every day that the pregnancy is prolonged carries with it an increased risk to both. Owing to progressive placental involvement the attempt to carry the patient on in the hope of securing a stronger infant frequently defeats its own object.

Irrespective of the stage of pregnancy reached, if the response to treatment is unsatisfactory, as shown by a steadily rising blood-pressure, increasing œdema and progressive albuminuria, immediate termination of pregnancy is advisable. Similarly, if symptoms have been present for more than four weeks, even if they have been milder and less progressive in character, interruption of the pregnancy should be considered In neither of these groups of cases should the interests of the child be allowed to outweigh the probability that prolongation of the pregnancy may inflict irreparable damage on the mother's vascular system. The case for termination of pregnancy may be stated in another way. It will be recalled that in approximately one case in four toxæmia will recur in a later pregnancy, which means that three patients out of four may look forward to subsequent pregnancies being uncomplicated in this way The possible disappointment

general disturbance of the patient which follows drastic purgation has adequate compensating advantages. Again, the value of forced sweating either by drugs or by the use of hot packs or blankets is open to question in view of the fact that nitrogenous products are not eliminated in this way. Similarly, although an increased urinary output is a welcome indication of improvement, it has been shown that this cannot be forced by an increase in the fluid intake nor, with the exception of hypertonic sugar solutions, by the use of diuretic drugs and such measures may be actively harmful. In cases in which the urinary output is seriously diminished, whether in pre-eclampsia or eclampsia, the intravenous injection of 500 to 1000 c.c. of a 20 per cent. solution of glucose two or three times daily is a valuable therapeutic measure.

Vaso-depressor Agents.—Since the manifestations of toxæmia are closely related to the underlying hypertension, it is natural that the effect of a wide range of drugs including bromides, iodides, nitrites, veratrone, and various endocrine preparations, has been tried in an effort to reduce the blood-pressure level. It may be said at once that, with the possible exception of veratrone, the reports on which are conflicting but on the whole not unfavourable, the action of these drugs is of doubtful value and at best temporary in effect On the other hand, many obstetricians have pronounced favourably on the results of thyroid extract, especially in the case of the obese patient with a low metabolic rate.

Against the adverse verdict which in general must be pronounced on the value of drugs in combating high blood-pressure must be placed the hope aroused by the work of Page [36] and his collaborators on the use of tissue extracts in the treatment of hypertension. Reference has already been made to the important investigations of Goldblatt [28] on the experimental production of hypertension. These studies have stimulated further research, one result of which has been the extraction by Tigerstedt and Brigmann [37] of a pressor substance from the kidney termed "renin." Subsequent investigations, in particular by Page [37] and by Grollmann,[38] have led to the extraction from the kidney of a depressor substance which is antagonistic to the pressor principle, and which is effective in reducing not only the artificially raised blood-pressure in animals, but also hypertension in man Page has recently reported the results of the employment of this substance in seventeen hypertensive patients; in the majority the downhill course of the disease appeared to be arrested, and in

Treatment of Eclampsia

Extended experience of the conservative method of treatment in eclampsia, advocated first by Stroganoff and the Dublin School, has fully confirmed its advantages over the radical measures formerly in vogue. The general principles of treatment comprise (1) the relief of intracranial tension, (2) the avoidance and treatment of cardiac and respiratory failure, and (3) judicious obstetric interference.

Relief of Intracranial Tension. — The prognosis in eclampsia is closely related to the intensity and duration of the convulsive crisis. So long as it continues the outlook is necessarily grave, whereas its disappearance is generally followed by rapid recovery. Its control is therefore a primary consideration in treatment, and measures directed towards improving the cerebral circulation and reducing cerebral œdema, the factors on which increased intracranial tension depends, are of the first importance. Here it is necessary to emphasise that while the height of the blood-pressure is an accurate index of the severity of the disease, the artificial lowering of pressure by the indiscriminate use of drugs or venesection may have harmful side-effects which on balance are disadvantageous. There is little to be gained from a reduction of blood-pressure *per se* without removing its cause, and not infrequently such measures lead to a dangerous circulatory collapse. Again, lumbar puncture, which might appear to be a rational means of reducing intracranial tension, is open to objection on account of the disturbance it causes, and in practice the procedure has not proved helpful

By contrast, the rational use of hypertonic sugar solution and of magnesium sulphate as recommended by Stroganoff represent a notable advance in treatment. The virtue of the hypertonic solution lies in its dehydrating effect, and the injection intravenously of from 500 to 1000 c c. of a 20 per cent solution of glucose two or three times daily is generally followed by a profuse diuresis and by an obvious reduction in œdema, with a corresponding improvement in the cerebral disturbance and the patient's health generally

A wide range of drugs, including in particular morphia, chloral hydrate and the barbiturates, may be employed for their sedative effect on the central nervous system. Of these morphia is probably the most dependable in its action, and during the convulsive stage it may be given in doses of gr ¼ every two to

inherent in interference at an early stage of pregnancy may therefore be compensated by a complete recovery and favourable future prospects, whereas unwise conservatism may not only fail in its object but may leave a legacy of invalidism which in itself makes further pregnancies unsafe.

The effect of pregnancy on the chronic nephritic is, as has been stated, almost uniformly adverse. In a woman with active symptoms of chronic Bright's disease pregnancy should be discouraged, and if conception occurs abortion is fully justified. Even when the condition is well compensated she runs a grave risk of shortening her life, offset at best by not more than an even chance of obtaining a living child. Pregnancy should be allowed to continue only after the risks have been explained to and accepted by the patient. It is true that in a minority of cases the added burden of pregnancy is well borne, but at any stage an aggravation in symptoms may necessitate immediate interference without consideration for the child. On the other hand, in contrast to the pre-eclamptic who may look forward to further pregnancies, the obstetrical future of the severe chronic nephritic is practically hopeless. This is her one chance of a living child, and if she is a primigravida a little greater latitude may be permissible than in a case of toxæmia of similar severity. If she already has living children the uterus should be evacuated without delay.

The method employed to terminate pregnancy is determined by the stage the pregnancy has reached, the severity of the symptoms and the rapidity with which they are progressing, bearing in mind that in all the cases the subject is poor surgical risk. In the early months the choice is between abdominal hysterotomy and induction of abortion, according to whether the pregnancy has advanced beyond the tenth week or not, and in the later months between induction of labour and Cæsarean section. If the cervix is taken up and the uterus reacts well to abdominal palpation, puncture of the membranes following sensitisation with quinine and supplemented by pitocin should be employed. If, on the other hand, the cervix is long and firm and the uterus sluggish, or if the severity of the symptoms is increasing so rapidly that immediate evacuation is necessary to anticipate the onset of eclampsia, Cæsarean section under gas and oxygen or local anæsthesia should be performed. Incidentally, where further pregnancy must be forbidden, hysterotomy or Cæsarean section provides an opportunity for effecting surgical sterilisation.

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A wide range of drugs, including in particular morphia, chloral hydrate and the barbiturates, may be employed for their sedative effect on the central nervous system. Of these morphia is probably the most dependable in its action, and during the convulsive stage it may be given in doses of gr. ¼ every two to

three hours until the seizures are controlled, unless respirations drop to 12 per minute. Chloral hydrate, which Stroganoff has recommended warmly, has long been used *in general medicine* for its sedative action on the central nervous system, and in addition *to morphia hypodermically, 30 grs. may* be given *per rectum* every six to ten hours. The barbiturate group of drugs are powerfully anti-convulsant in their action, but have the disadvantage of being respiratory depressants, except in moderate doses, and on this account should be used with caution, especially when given intravenously The possibility of untoward reactions, especially on the respiratory and circulatory systems, necessitates circumspection in the use of all sedative drugs in eclampsia. The drug used and the amount given must vary according to individual requirements, and so far as can be judged not more than a minimal effective dose should be employed.

The avoidance of peripheral stimuli which may excite the irritable central nervous system and precipitate a convulsion, is *widely recognised* as an essential principle in treatment. The room is darkened and kept as quiet as possible, and the patient shielded as far as practicable from any kind of disturbance except such as is unavoidable in the course of treatment. Hypodermic and intravenous injections, as well as such nursing details as attention to the bladder and bowel, should as far as possible be carried out immediately after a convulsion, that is when the patient is deeply unconscious. Routine gastric and colonic lavage with a bicarbonate of soda solution may be indicted as a form of treatment which causes disturbance out of all proportion to any possible benefit The hope of eliminating a hypothetical toxin by this *means* is illusory, and to attempt in this way to control vomiting which is probably of cerebral origin, is equally irrational *Moreover, acidosis is neither a common nor* a prominent feature in eclampsia, and if it is present should not be treated *by sodium salts for reasons already stated.* If the patient is constipated, enemata should certainly be employed, but routine washing out of the stomach *and bowel is a harmful* ritual which might well be discontinued

Prevention and Treatment of ***Circulatory*** **and** ***Respiratory*** **Complications.**—It is necessary to recognise the possible development of two distinct types of circulatory failure in *eclampsia*, central and peripheral, the appearance of either of which adds materially to the gravity of the prognosis. Together with respiratory complications, circulatory failure accounts for almost

one-half of all the deaths in eclampsia. Whether or not the myocardium is directly affected by the toxæmia, as such, is doubtful. On the other hand, it is clear that the rapidly developing hypertension of severe pre-eclampsia places a heavy burden on the left ventricle, and that the sudden rise in pressure and increased demands associated with the convulsions of eclampsia may lead to serious cardiac embarrassment. At the same time, the development of pulmonary œdema, due either to left ventricular failure, or to the toxæmia itself, is frequently an additional handicap. The appearance of cardiac asthma, together with a fall in blood-pressure, sudden or gradual, and unaccompanied by other signs of improvement, are clear indications of left ventricular failure accompanied by acute pulmonary œdema and are signs of grave significance.

The treatment of this type of cardiac failure comprises such measures as dehydration by the infusion of a concentrated sugar solution, the judicious use of oxygen, rapid digitalisation, the cautious administration of morphia, and the slow removal of 500 c.c. of blood. This is one of the few indications for venesection in eclampsia. At the same time, if the patient is unconscious it is obviously necessary to prevent such additional respiratory and cardiac embarrassment as may result from the aspiration of a denture or of saliva or vomited material, or from the jaw or tongue falling back and, as Holland[39] puts it, all the arts of the anæsthetist should be employed to secure and maintain a free airway during the comatose stage.

Failure of the peripheral circulation must be distinguished from myocardial failure, and may arise from a number of causes acting independently or together. In many cases it is precipitated by shock-producing agencies, such as pain or the trauma of a difficult or operative delivery. Loss of blood in the course of delivery or associated with accidental hæmorrhage or an injudicious venesection may also be causative factors. Over-dosage with barbituric derivatives and chloroform anæsthesia favour its occurrence. The symptoms are closely similar to those of obstetric shock, and again the most significant sign is a steady fall in blood-pressure unattended by other evidence of improvement.

The treatment of this form of circulatory collapse is closely similar to that of obstetric shock with this important addition, that if these symptoms should appear, as they may, before delivery, every effort must be made to avoid such aggravating

factors as trauma and blood loss during the birth of the child. Warmth, slow transfusion with blood or hypertonic glucose, the judicious use of cardiac or respiratory stimulants, and delivery by the most conservative means possible, comprise the main principles of treatment.

Obstetric Interference. — Extended experience of the conservative methods of treatment advocated by Stroganoff and the Dublin School has fully confirmed its advantages over the more radical methods formerly in vogue. This, however, is a generalisation which admits of certain exceptions. In the first place, it is generally agreed that after the cervix is fully dilated, delivery should be completed promptly in the most appropriate way to avoid the further elevation of blood-pressure and strain on the heart incident to the second stage of labour. In the second place, in antepartum eclampsia if the cervix is taken up and the response of the uterus likely to be satisfactory, it is probably advisable to induce labour by puncture of the membranes. Obstetric opinion on the wisdom of this procedure is by no means unanimous, and it may be argued that the disturbance caused by the induction and by labour itself must have an unfavourable effect on the toxæmia. This consideration is offset by the fact that as a general rule improvement follows delivery, and on balance induction seems justifiable. In the third place, and still more debatable, is the question of when, if ever, eclampsia by itself justifies the performance of Cæsarean section. No rigid rules can be laid down except that it is unnecessary in the milder type of case and out of the question in cases in which the blood-pressure is falling rapidly or other indications of impending circulatory failure are present. In the absence of such contra-indications, Cæsarean section may be considered in severe cases that are not responding to treatment and in which the cervix is long, firm and closed, or where from some other cause vaginal delivery is likely to prove difficult

The manifestations and side-effects of eclampsia vary so widely from case to case both in character and degree that its management exercises to the full the knowledge, judgment, and finesse of the attendant. It is therefore futile to attempt to lay down any scheme of treatment which may be applied as a routine without important reservations and modifications to satisfy individual requirements The general principles of treatment applicable to a case of average severity may, however, be summarised as follows . —

(1) *General Treatment.*—The patient is isolated in a quiet, dark room and not disturbed in any way, except for necessary purposes of treatment. A retention catheter is passed and the urinary output measured two hourly, together with the blood-pressure level, temperature, and the pulse and respiratory rates. Constant observation by doctor and nurse is necessary. The lower bowel is cleared by an enema, but gastric and colonic lavage are omitted.

(2) *Sedative Treatment.*—Morphia gr. ¼ is given at once, and is repeated every three hours until the seizures subside, unless the respiratory rate drops to 12 per minute. Chloral hydrate grs. 30 is given per rectum every eight hours. Twenty c c. of a 10 per cent. solution of magnesium sulphate are injected slowly intravenously, and may be repeated after twelve hours; if œdema is marked, 500 c c. of a 20 per cent. glucose solution may also be given by the same route. Saline infusions are strongly contra-indicated, as are also sodium-containing drugs in any form.

(3) *Treatment of Circulatory and Pulmonary Complications.*—To avoid respiratory embarrassment, maintenance of a free airway is essential. Dentures are removed, and during the comatose stage the aspiration of mucus or vomited material is prevented by posture and clearance of the air passages. Pulmonary œdema associated with left ventricular failure is treated by intravenous glucose, the slow withdrawal of 500 c c. of blood, oxygen and digitalisation If there are indications of peripheral circulatory collapse, shock therapy is instituted.

(4) *Diet*—Nothing is given by mouth until the patient is fully conscious. Thereafter she is given water and fruit juices and milk, proceeding cautiously as the diuresis increases and her general condition improves.

(5) *Obstetric Treatment.*—If the cervix is taken up and the uterus hardens on abdominal palpation, labour is induced by puncture of the membranes. After the cervix is fully dilated delivery is completed in the most appropriate way. Cæsarean section may very rarely be performed in the severe case which is not responding well to treatment and in which the reaction to induction is unlikely to be satisfactory In view of its action on the vascular system the ergot group of drugs should not be employed post-partum.

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SOME ASPECTS OF ŒSTROGENIC THERAPY

By W. F. T. HAULTAIN, O B E., M C., B A., M.B., F.R C.S.Ed., F.R C.O.G.

I HAVE chosen the subject of œstrogenic therapy for this lecture for several reasons. The first is that the discovery of the female sex hormones is of comparatively recent origin and, though no doubt there is still much to be discovered with regard to sexual physiology, the work on the natural and synthetic œstrogens has advanced rapidly, with the result that various preparations are even now of the greatest use to the clinician. Secondly, œstrogenic therapy has always been of particular interest to me, even long before I had heard of such a name, and in 1928 I wrote a paper [1] on the administration of ovarian extract for the artificial menopause, gleaned from work which I had been carrying out clinically for five years previously. Since that time I have continued my clinical observations with the various natural and synthetic œstrogenic products which have been introduced, and in this lecture I intend to include my further observations in their appropriate place. Thirdly, special work in the clinical use of œstrogens has been carried out during the last three years in my obstetrical and gynæcological wards. That being so, I intend to deal chiefly in this lecture with conditions with which I have had some clinical experience in regard to the value of œstrogens, and will do no more than refer to other conditions for which œstrogens have been recommended, of which I have no personal experience. My last reason in choosing this subject is contingent on my first, in so far as œstrogenic therapy is now comparatively cheap and can often be carried out by the general practitioner in his practice. It is therefore an eminently suitable subject for a post-graduate lecture, in which I can discuss the various conditions for which œstrogens are useful and the type of products which can be best used. Some idea of the dosage required in the different conditions will be given and the benefit to be expected with such dosage. It must be remembered, however, that this therapy is still in its pioneer stage, and ideas regarding dosage

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may change materially in the ensuing years. Lastly, I would like to give some warnings regarding the dangers that must be avoided in some particular conditions before subjecting a patient to such a therapy or applying it for too long a period of time.

Historical Account of Discovery of Œstrogens

It may be of interest in the first place to give a short historical account of the discovery of the more common œstrogens, including short descriptive notes on the most important preparations which are used clinically; to many of us these are just a collection of names, which are confused in our minds with the numerous trade names allotted to the same substance by the various manufacturers. In my opinion it should be forbidden by law for any substance to be called by more than one name, as this heterogeneity of names for any important substance is an added load to the already overburdened doctor's brain, and in many cases allows proprietary drugs to be prescribed without any knowledge as to their true nature. Especially is this the case with regard to the medical student's knowledge of proprietary preparations.

In 1896 Knauer demonstrated that ovarian transplantation following double oöphorectomy prevented atrophy of the uterus, and thus showed that the ovary must produce an internal secretion which acted through the medium of the blood stream. It was not until 1912, however, that Adler added further contribution on the physiology and pathology of the ovarian function,[2] and Frank and Rosenbloom contributed additional knowledge in a paper in 1915 on the physiological active substances contained in the corpus luteum and placenta[3] The war years prevented much further research on these lines, and it was not until 1923 that rapid progress was made, owing to the discovery by Allen and Doisy[4] of the vaginal smear reaction in detecting the presence of œstrogenic substances. After this Frank and his collaborators found that a definite ovarian hormone was present in circulating and menstrual blood, the quantity passing through a definite cycle corresponding to the menstrual cycle. They also found this hormone in the blood of pregnant women, in the placenta in large quantities, and even in the corpus luteum itself In 1927 a further impetus was given to the research by the discovery of Aschheim and Zondek[5] that œstrogens were present in high concentration in the urine of pregnant women, and later of mares. At this time it was believed by the majority of observers

that the ovary produced only one hormone, and it was not till 1928, when the first natural œstrogen was obtained by Doisy, Veler and Thayer [6] from pregnancy urine and was isolated in crystalline form by the same collaborators [7] in 1929, and at the same time Corner demonstrated a different hormone from the corpus luteum, that it was really definitely established that the ovary produced two entirely different hormones. Doisy named his crystalline substance theelin, but it is now universally recognised as œstrone, which is a hydroxyketone having the formula $C_{18}H_{22}O_2$. Later, two other common œstrogens were prepared from pregnancy urine and also from the placenta, and these were named œstriol (trihydroxyœstrin $C_{18}H_{24}O_3$) and œstradiol (dihydroxyœstrin $C_{18}H_{24}O_2$).

It is interesting to note that in 1932 a natural œstrogen equilenin was prepared from the urine of pregnant mares by Girard, Sandulesco *et alii* [8]; in 1938 Bachmann [9] synthesised equilenin, this being the first sex hormone to be entirely synthesised from simple materials.

In 1932 Cook, Dodds and Hewett [10] prepared the first œstrogenic substance synthetically (1-keto-1 : 2 : 3 : 4 tetrahydrophenanthrene), but this was of relatively low potency and at that time these investigators stated that there were grounds for believing that substances of much higher activity would be found before long; their prophecy was certainly a correct one, for in five years substances were discovered, 300,000 times more active than the initial preparation. In 1936 Dodds and Lawson [11] showed that the phenanthrene ring, which had been present in all the earlier synthetic œstrogens, was not necessary for œstrogenic activity and that numerous diphenyl derivatives had œstrogenic properties. Further simplification of the molecule led to the examination of anol (*p*-hydroxyprophenyl benzene), and the high activity of this substance was found to be due to an impurity [12]; thus the œstrogenic value of the impurity must be of very high potency. Further investigation of this contaminant at the Courtauld Institute produced hexœstrol, whereas at about the same time stilboestrol (4-4 dihydroxy α-β diethylstilbene) was produced by the same workers collaborating with Professor Robinson and his co-workers at Oxford [13, 14, 15]. These two substances were found to be highly œstrogenic by oral administration and compared favourably with the activity of œstradiol by injection.

In 1937 Robson and Schonberg [16] discovered another œstro-

may change materially in the ensuing years. Lastly, I would like to give some warnings regarding the dangers that must be avoided in some particular conditions before subjecting a patient to such a therapy or applying it for too long a period of time.

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(7) In large doses they inhibit lactation, probably by depressing the action of the lactogenic secretion upon the breast.

(8) They promote the growth of the nipple and the mammary gland.

It is of the greatest importance before administering œstrogens to be sure that the therapy is based on a sound appreciation of the physiological principles involved. They should never be given in a haphazard fashion for conditions outwith the indications just given, otherwise much harm may result in the way of upset of menstrual and metabolic functions (irregular bleedings, etc.). Prolonged dosage may produce underactivity of the ovary and sterility by inhibiting the anterior pituitary, and this has to be considered, especially in the treatment of secondary amenorrhœa, when prolonged treatment may do more harm than good if not given in cycles to correspond with the pre-ovulatory phase. Care has also to be taken in the administration of œstrogens to women whose menstrual cycles are normal, *e g.* for skin conditions, as the menstrual upset may be serious ; if given for such cases they should be administered only in the post-menstrual and proliferative phases of the cycle, when usually no harm results. There is no doubt that all œstrogens have carcinogenetic properties, but the dosage employed is relatively so small that this danger would appear to be negligible. This property, however, should act as a deterrent in giving prolonged treatment over months or even years, which in my experience is hardly ever required if permanent benefit is to be achieved by the treatment.

Methods of Administration and Dosage

The natural œstrogens were at first administered orally by tablets, or parenterally in aqueous solutions, but it was found that in order to get the satisfactory results by large dosage which is required in some conditions, parenteral administration of the benzoate œstradiol esters in oil was much more efficacious. In these earlier days the dose of œstrone was reckoned in international units and the œstradiol ester in international benzoate units, the unit depending on biological tests, but as the criterion adopted by each worker varied it was impossible to correlate results and chaos ensued. The Committee on Sex Hormones of the League of Nations Permanent Health Commission laid down

genic substance in triphenylchloroethylene, which was found to have a marked degree of activity and has been successfully used in the treatment of many of the conditions to be mentioned in this lecture. In further reference to this œstrogen in this paper the name will be abbreviated to T.P.E., and I am indebted to Dr A. I. S. Macpherson for all the work done in my wards with this substance.

Assessment of Results

It has been shown by Papanicolau and Schorr [17] that the activity of the œstrogens in the human can be estimated by the change in the vaginal smear, large flat squamous epithelial cells with pyknotic nuclei being in abundance with a characteristic leucopenia and cornification of the cells, but for practical purposes it has been shown by Smith [18] and others that alteration in the smears is usually preceded and always paralleled by the relief of symptoms. Smears have been taken in some of my cases to show the beneficial action of œstrogens, but I am afraid that in the majority of cases the efficiency of the œstrogen has been estimated by the relief of symptoms and by clinical cure of the condition.

Effects of Œstrogens and their Dangers

The effects of œstrogens can be summarised as follows :—

(1) They increase the size and vascularity of the uterus and stimulate the proliferation of the endometrium in preparation for the action of progesterone
(2) Bleeding will occur from endometrium released from the influence of œstrogens—œstrin withdrawal bleeding
(3) They increase the spontaneous activity of the uterine and tubal muscle and also the reactivity of the myometrium to oxytocins.
(4) They increase the vascularity of the vagina and vulva, and the cornification of the vaginal epithelium
(5) Inhibition of the activity of the anterior lobe of the pituitary.
(6) Vasomotor, metabolic and psychical disturbances characteristic of the menopause may occur when the body is deprived of œstrogen

on account of its lower threshold activity, but it would appear that its action is equally efficacious, and toxic side-effects, such as nausea, are almost unknown. For purposes of comparison the single dosage of stilboestrol varies from 0·5 to 5 mgm. according to the strength required to treat the condition, whereas T.P.E. is given in oral dosage of 200 to 800 mgm., and by injection 250 to 300 mgm. Further, it would seem that the action of 5 mgm. stilboestrol given orally compares with 1 mgm. œstradiol benzoate by injection, and *1 mgm. stilboestrol given orally* compares with 5 to 6 mgm. œstradiol orally[20]; 400 mgm of T.P.E. given orally compares with 1 mgm. œstradiol benzoate by injection.[21]

Uses of Œstrogen Therapy

As I have previously referred to the great importance of using œstrogens only when one is sure that the therapy is based on sound physiological knowledge, it will be best to refer to the main conditions which can be treated under the headings of the effects of œstrogens previously summarised.

1. *Use in Cases of Uterine Hypoplasia in order to Stimulate Growth*

Œstrogens have been used with some beneficial results in cases of delayed or scanty menstruation in girls under twenty years to try and stimulate the growth of the uterus and its mucosa. Administration should be restricted to from ten to fourteen days every month so as to try and simulate the œstrone producing period of the cycle, and if menstruation is occurring should only be given during the post-menstrual and proliferative phases. Œstrogens can also be employed with benefit when dysmenorrhœa is due to a hypoplastic uterus. The dosage varies greatly, but 1·5 mgm. stilboestrol or ovendosyn * daily is the maximum, and, in my opinion, the results can be aided by the simultaneous administration daily of 1 gr. thyroid extract, which, however, is continued through the whole cycle. Treatment has usually to be kept up for several months if any chance of a beneficial effect is to be obtained. I have found the treatment to be of little value if given to cases over twenty years of age, and other writers seem

* Pills containing stilboestrol 0·5 mgm. and calcium 227 mgm (Menley and James).

as the international unit for œstrone the activity of 0·0001 mgm. of a standard preparation, and the international benzoate unit as the activity of 0·0001 mgm. of œstradiol benzoate, and so it has come to pass that the natural œstrogens are now prescribed in milligrams, 1 mgm. œstrone equalling 10,000 international units and 1 mgm. œstradiol benzoate equalling 10,000 international benzoate units. It was found by Mazer and Israel[19] that 0·1 mgm. of œstradiol benzoate when injected maintains the normal level of œstrogen in the blood for four days, as reflected by the amount passed in the urine, and that 0·5-1 mgm. causes a temporary excess of œstrogen in the blood, reaching the normal premenstrual amount on the fourth or fifth day after administration. They also showed that no matter what amount be injected it was all excreted by the fifth day after the injection, and that the minimum daily dose of œstrone or œstradiol capable of maintaining the premenstrual blood level in a castrated woman was as low as 0·05 mgm., or, if given parenterally, 0·1 mgm. every fourth day. It may be that the estimation of œstrogens by finding the amount passed in the urine has little relation to the actual blood content, but from my clinical experience, referred to later, it would seem that the amount required to prevent menopausal symptoms occurring in a castrated woman is little more than that found experimentally by Israel and Mazer. These workers also showed that with the majority of natural œstrogens parenteral administration is at least twice as active as oral, but with œstrone the parenteral activity is not so great in proportion. Thus, until recently, parenteral administration was most frequently used when large dosage was required, especially as its absorption could be more accurately estimated; now, however, when synthetic œstrogens can be given orally with accuracy and efficacy, this mode of administration is more commonly used and is easier and cheaper. Thus œstrogenic treatment is now brought within the reach of all. Natural œstrogens can also be administered vaginally in the form of pessaries and are probably best given in this way when the condition to be treated is local and no interference with the menstrual cycle is desired. Œstrogenic ointments are also prepared for use in skin and irritative conditions. The synthetic œstrogens are usually given orally, but T.P.E. is equally effective by injection, and at present a suspension injection is being tried with a view to retarding the absorption and thus prolonging the action. The dosage of T.P.E. is much greater than stilboestrol

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were painless. At a later date, when œstrogens became better understood, many clinicians have again endeavoured to induce labour with large doses of œstrogens followed often by the administration of pituitary extract, but with most disappointing results. Œstrogens, however, have been tried by many clinicians in cases of uterine inertia, and Jeffcoate [23] has published results where success was attained in overcoming the inertia in over 50 per cent. of cases of primary inertia where there was no demonstrable cause for the inertia. The dosage he recommends is 2 mgm. of the benzoate ester injected hourly for ten hours, and he warns that no apparent benefit is usually discernible until after several injections have been given. It is difficult to assess, therefore, the full value of the œstrogen in these cases as the inertia is often cured within ten hours without any œstrogenic treatment. He suggests that in cases in which inertia is expected to occur the œstrogen may be given twice daily in similar dosage during the last two weeks of pregnancy.

I have little experience in the administration of œstrogens for inertia, but during the last eighteen months all cases of missed abortion which I have seen have been treated with T.P.E. Ten cases of missed abortion, proved by a negative Aschheim-Zondek reaction and the cessation of uterine growth, were thus treated, and 2 to 3 gms. T.P.E. were administered daily for seven days, if need be. Two cases aborted completely within this time, and four others after castor-oil and three injections of 0·5 c.c. pituitary extract had been given on the eighth day. Three others aborted after the pituitary had been given, but the abortion was incomplete and operative treatment was required for the removal of the retained products. There was one complete failure, but this case at curettage appeared to be a case of incomplete abortion and therefore should not probably have been classed as a missed abortion. Similar treatment was tried in a case of induction of abortion at the fourth month for advanced disseminated sclerosis in whom, if at all possible, operative treatment was contra-indicated; but, though T.P.E. was given for three weeks with several attempts at further induction with pituitary extract, the nearest approach to abortion was some severe pains which were accompanied only by a brownish discharge.

to agree with this. Some recommend that progesterone should be given in the premenstrual phase, which is theoretically sound, but I have no personal experience of this addition.

2. *To Promote Uterine Bleeding in Cases of Secondary Amenorrhœa*

It might be thought that œstrogens would be of great value in cases of secondary amenorrhœa, and in mild cases they often succeed, but failure is more common than success, and probably better results are obtained by the use of anterior pituitary preparations which act directly on the ovarian function. If œstrogens are to be tried they should be given as for the cases of hypoplasia, namely, only in the post-menstrual and proliferative phases; they should not be used in too large dosage or for too long, as the inhibitory action on the anterior pituitary with excessive dosage must be remembered, and the œstrogen may thus do more harm than good Personally, I usually give 1·5 to 3 mgm. stilboestrol or ovendosyn daily from the tenth to the fourteenth day of the cycle in the more severe cases, but much less may be efficacious in cases where the amenorrhœa is of short duration. Bleeding nearly always occurs within fourteen days of stopping the œstrogen, but when the treatment is discontinued no further periods may result, the previous bleedings having been due to œstrin withdrawal and not to the establishment of a regular menstrual cycle. The most satisfactory cases to treat under this heading seem to be those of delayed menstruation following the post-natal period when œstrogens in quite small doses often give a quick and permanent result Some clinicians recommend progesterone in cases of secondary amenorrhœa as well as an œstrogen.

3. *To Increase the Activity and the Sensitivity of the Uterine Muscle*

As long ago as 1927 Addis[22] stated that ovarian extract without corpus luteum by injection caused painless contractions of the pregnant uterus, and in a number of cases he was able to induce labour with such injections. This statement regarding the induction of labour was not corroborated by other workers, myself included, but there was no doubt that by giving this extract the uterine contractions were markedly increased but

these cases of senile vaginitis and kraurosis complete relief was obtained in 40 cases, 6 were very much improved, and 3 failed to benefit. The œstrogens used were as follows: progynon forte * in 26 cases either alone or with progynon dragees orally or/and with Kolpon pessaries † with 20 complete cures, 3 cases being very much improved and 3 showing no benefit. The treatment consisted of an injection of 5 mgm. progynon forte twice weekly for 5 injections, during which time one dragee (0·1 mgm.) was given three times daily and Kolpon pessaries were inserted one nightly from the tenth to eighteenth day of the treatment. Twelve cases were cured by one course of treatment, 7 by two courses, and 1 required three courses before complete relief was effected Progynon dragees alone effected a cure in 2 mild cases and Kolpon pessaries alone cured another mild case. Stilboestrol dipropionate was used in 10 cases with 9 complete cures, and 1 case was very much relieved, the latter having only received the small dose of 6·3 mgm. Cure was attained in the majority of cases by giving 5 mgm. three times a day for a week, but 1 case required two weeks' treatment before being relieved entirely. Dr Macpherson has treated 9 cases with T.P.E. with 7 cures and 2 cases were very much relieved; he has also treated 1 case with triphenylmethylethylene with complete relief. In the majority of these cases individual doses of 250 mgm. were injected to a total dosage of from 250 to 3500 mgm. In 2 cases oral administration was given alone with a 400 mgm. dosage, cures being obtained with a total of 40,000 mgm. and 50,000 mgm. respectively. All 3 cases of leukoplakia were cured, T.P.E. being used in 2 cases and stilboestrol in one case in similar dosage to the above.

It is seen from these statistics that 88·5 per cent. were completely cured, and only in 5·8 per cent. was there no cure or considerable benefit achieved. This would seem to prove that œstrogenic therapy is of great benefit in the treatment of these conditions; I would, however, like to issue a caveat: if the vaginal discharge persists after two weeks' treatment or recurs soon after the treatment is finished, it is essential that a diagnostic curettage should be performed to exclude cancer of the body of the uterus. Within the last three years I have seen 3 cases of carcinoma of the body of the uterus, in whom the only clinical feature was apparently a senile vaginitis; and I have made a

* Œstradiol ester in oil (Schering)

† Pessaries containing œstrone 0·1 mgm. with 70 per cent. glucose (Organon).

4. *To promote Proliferation of the Epithelium of the Vagina and Vulva*

Œstrogens have been found to cause extensive proliferation with cornification of the surface layers of the vaginal mucosa. The cells are filled with glycogen, which helps to maintain the vaginal acidity and to resist infection. It is possible also that a phagocytosis is stimulated in the subepithelial layers. In the vulva also there is increased vascularity and improved vitality with resultant stimulation of epithelial growth and increased resistance to infection. From these physiological facts œstrogens have been used for several atrophic or infective conditions of the vagina and vulva occurring especially outwith the child-bearing period, such as kraurosis vulvæ, senile vaginitis, leukoplakia in elderly women and vulvo-vaginitis in prepubertal girls, and it is in such conditions that some of the most beneficial therapeutic results with œstrogens have been obtained. Previous to the discovery of œstrogens the treatment of kraurosis and senile vaginitis was most unsatisfactory. Complete cures were seldom effected and palliative measures had to be constantly prescribed. Leukoplakia was also difficult to treat by conservative measures, and operative treatment was frequently required. Œstrogen therapy has changed the situation entirely, especially with regard to senile vaginitis and kraurosis, and, instead of these conditions being almost incurable, they are now usually easily cured by a few weeks' treatment and symptoms do not recur unless fresh infection occurs, even though the vagina and vulva return to their atrophic state within six weeks of the cessation of treatment

I have been able during the past few years to collect 49 cases of senile vaginitis and kraurosis vulvæ (Table I) and 3 cases of leukoplakia vulvæ which have been treated by œstrogens Of

TABLE I

Senile Vaginitis and Kraurosis.

	Total	Cured.	Very Much Improved	Failed
Progynon forte alone or with dragees and/or Kolpon pessaries	26	20	3	3
Kolpon pessaries alone	1	1		
Progynon dragees alone	2	2	.	-
Stilboestrol dipropionate	10	9	1	
T P E.	9	7	2	
Triphenylmethylethylene . .	1	1		
	49	40	6	3

symptoms, and H. R. Donald,[25] using natural œstrogens and their esters, reports good results in 94 cases, recommending 0·3 mgm. thrice daily as an average dosage, though in mild cases 0·3 mgm. a day was sufficient. In more severe cases 1 mgm was injected thrice weekly as well as 0·3 mgm. daily orally, and in three very severe cases 5 mgm. had to be injected twice weekly. E. C. Smith[18] reports on 77 menopausal cases treated with synthetic œstrogens, giving a dosage somewhat similar to Donald's; 58 were cases of the natural menopause, 15 were post-operative and 4 post-radiational. He obtained excellent results in 70 per cent.; 21·7 per cent. required a second treatment and 8·3 per cent. several treatments. He states that the symptoms after an artificial menopause are more difficult to control, and 15 of his 19 such cases did not respond to treatment immediately.

I have little experience in treating cases of the natural menopause, as these cases are generally treated by the family doctor or sent to a physician, but I have had a large experience of cases of artificial menopause following hysterectomy with removal of both ovaries or following treatment with radium. As stated previously, I published a paper on the action of ovarian extract in 31 post-operative cases in 1928,[1] and was so impressed with the value of ovarian extract in preventing severe menopausal symptoms, that since then every case from whom I have removed both ovaries and who were operated upon before or at the menopause has received œstrogenic therapy. I have collected almost 600 such cases, and though a detailed investigation has not been carried out as in my previous paper, practically every case was seen three months after her operation and was questioned regarding any menopausal symptoms, so that the effect of the œstrogen could be estimated and the dosage regulated; if any menopausal symptom occurred or recurred, the patient was asked to report in a further three months. I am satisfied that menopausal symptoms occurred in very few cases, and if they did occur were practically never of any marked severity. The only disturbance that may be difficult to prevent in many cases is adiposity, and this is not usually at all gross. Therapy has practically always been started on the fifth day after operation, after the patient has got over any operative sickness and discomfort by the action of purgatives, and I have used various preparations of œstrogens as they have been discovered. For many years I used progynon dragees, giving at different times from 0·075 to 0·125 mgm. three times daily for three months, by which time I was usually able to

habit of curetting all cases of profuse post-menopausal vaginal discharge, whether bloodstained or not, even when associated with the other signs of senile vaginitis, before starting any conservative treatment with œstrogens. Likewise, in a case of leukoplakia one has to remember, in the first place, that all such cases are not benefited by œstrogens, as the condition may be due to several other causes, such as glycosuria, lack of free hydrochloric acid in the stomach preventing absorption of essential vitamins, etc.; and, in the second place, that all cases treated with œstrogens must be watched carefully whilst under treatment lest cracks, fissures, or ulcers develop and persist, which are pre-cancerous. I have encountered one such case of carcinoma of the vulva which had occurred during prolonged treatment with an œstrogen before I was consulted.

Œstrogens orally, and especially in pessary form,* have proved to be most beneficial in cases of gonococcal vaginitis and vulvo-vaginitis in young girls, and many statistics of beneficial results have been published from time to time,[24] but I have had little personal experience of this use of œstrogens.

5. *To Inhibit the Anterior Lobe of the Anterior Pituitary*

Œstrogens have been prescribed in order to try to prevent premenstrual and menstrual headaches, which were thought in some cases to be due to an increased pituitary activity. I have tried this treatment in several cases with marked benefit, but in others, as one would expect, no improvement was noted. The œstrogen is given in fairly small dosage, not more than 0·3 mgm., for three days before the headache is to be expected; using this dosage the menstrual cycle is usually not interfered with in any way, and thus the treatment does at any rate no harm even if it should cause no benefit

6. *To prevent the Occurrence of Disturbances characteristic of the Menopause*

It was in this connection that œstrogens were used even before they had been discovered as definite entities, and it is probably for this reason at the present time that œstrogens are most generally prescribed by the general practitioner. Many papers have been written on the efficacy of different œstrogens for menopausal

* Special small pessaries for use in young girls are made by Schering containing 0·25 mgm œstradiol per pessary

7. *To Inhibit Lactation*

On the assumption that lactation is controlled by a hormone prolactin which is produced by the anterior pituitary,[26] it was thought that œstrogens might be used to inhibit lactation. As late as 1938 Jeffcoate[23] stated that œstrogens were of little practical use for this purpose, but this opinion has been refuted entirely during the last three years. Since 1938 all my patients at the Simpson Memorial Maternity Pavilion, who have required that lactation should be prevented or inhibited, have been treated with T.P.E. or with the stilboestrol preparations, ovendosyn and clinoestrol.* Macpherson and Robertson[21] published the results in 12 of these patients in whom lactation had been inhibited with T.P.E , but since then another 101 cases in hospital have been so treated by Macpherson and myself, making a total of 113 in all. The results are as follows :—T.P.E. was used in 80 cases, and in 55 of these it was given by injection, only one injection of 250 to 300 mgm. in 5 c c. oily solution being given for each case; in 52 of these patients there was complete inhibition of lactation, but in 3 secretory activity persisted ; in no case was there a recurrence of secretion after inhibition ; 6 suffered from painful breasts and 3 had mastitis, but in 2 of these the inflammation was present before the œstrogen was given. More recently 14 cases were treated by one injection of a T.P.E. dispersion in water (250.mgm. in 1 c.c), as it was thought that the effect might be more persistent with such a preparation owing to slower absorption ; in all the 14 cases lactation was inhibited ; 2 cases had mastitis before treatment was instituted. Eleven cases were treated with T.P.E. orally, giving 500 mgm. three times daily for two days and approximately 200 mgm. three times daily for two days ; lactation was inhibited in all 11 cases, though one complained of painful breasts and one developed mastitis. Recently, triphenyl methylethylene has been given orally, the dose being 50 mgm. three times daily for two days, twice daily for one day and once the next day ; 7 cases were so treated, and in 5 inhibition of lactation resulted, but *in 2 secretion persisted. Treatment with this* œstrogen is still in its experimental stage, and it is thought that better results will be achieved by larger dosage Stilboestrol (ovendosyn or clinoestrol) was given orally in 26 cases, 5 mgm. being given three times daily for two days, twice daily for one day and once the next day ; in 22 inhibition of lactation resulted,

* Stilboestrol dipropionate (Glaxo)

decrease the dosage gradually until no further treatment was necessary. Any obstinate cases, and they were seldom encountered, were *given injections of 1* mgm. of progynon forte twice weekly as well as the oral administration. Lately, I have been using stilboestrol dipropionate or ovendosyn, giving 0·5 mgm. twice daily and decreasing the dose gradually after three months. Very seldom has the initial dose had to be increased to check symptoms, and in most cases the treatment can be stopped entirely within six months. It would seem that œstrogenic function must be taken on to some extent by some other gland such as the suprarenal, which is possibly stimulated by the anterior pituitary. I have always as a routine used œstrogens in small dosage, and very seldom has any larger dose than the routine been required. Thus I disagree with Smith who, as previously stated, gave as his opinion that cases of artificial menopause were more resistant. *Possibly the difference in results is due to my beginning* the treatment very soon after operation and before the metabolism has had time to suffer from the sudden cessation of œstrogen production, œstrogens never having been entirely absent; in support of this view I would state that I have found it to be much more difficult to control the menopausal symptoms following a post-radiational menopause, and I think this is because one cannot begin treatment with œstrogens for at least three months after radiation lest the bleeding for which it was given recurs. I would agree with Smith that these cases often have fairly severe menopausal symptoms which may require a more intensive treatment with œstrogens to effect a cure. I have not found that younger patients who have suffered from a surgical menopause require any more intensive therapy than those of menopausal age—in fact, in my experience, the reverse has been the case, and it is the latter, if any, who require an increase of dosage. This corresponds with the recent findings of Mazer and Israel [19] already mentioned, who state that 0·05 mgm. per day is sufficient to keep the œstrogenic content of the blood normal, and it is thus quite possible that even a smaller dose than I am in the habit of giving would suffice in most cases.

I would, however, utter another warning regarding the over-treatment of natural menopausal cases with œstrogens as bleedings may recur, the positive diagnosis of which may require a diagnostic curettage, and I know of two cases in which hæmatometra has developed, for which hysterectomy had to be performed.

can be given immediately after the labour is over and the patient is not reminded of her loss by her breasts filling up or by any treatment being required to be instituted later to prevent them doing so. During the puerperium, however, probably oral administration is best, as the injection is oily, takes some time to give and may cause some discomfort during its administration; this disadvantage, however, may possibly be overcome by using the preparation of T.P.E. dispersion in water when only 1 c.c. is given. In my experience the cases which take longest to come under the effect of the œstrogen are the cases of abortion and premature labour from the twentieth to thirty-second weeks. If lactation recurs after treatment has been given, further treatment has, in my own experience, always caused complete inhibition and the œstrogen acts with great rapidity.

It can thus be seen from the above results that œstrogens are of the greatest use in the inhibition of lactation, and that probably in the future they will be used as a routine to produce this effect.

8. *To Promote the Growth of the Nipple and the Mammary Gland*

The use of œstrogens in chronic mastitis was suggested by Beckwith Whitehouse,[27] and I have treated several cases of this condition with success by means of œstrogenic therapy. The most dramatic case was that of a little girl aged twelve years who had been treated in another department for a year or more by every known conservative treatment with no beneficial result, and she was sent to me to see if any gynæcological hormonal treatment could be suggested before surgical treatment was carried out. She was in agony on account of an exquisitely tender breast which showed a localised induration about 1 inch in diameter, over which was a chronic ulcer. Dr Macpherson and I treated her with 400 mgm T.P.E. daily, which gave her almost immediate benefit, and within three weeks the breast appeared to be almost normal and there was no pain or tenderness. She was seen for several months after treatment had finished and again about a year later when she complained of a slightly painful nodularity in the opposite breast, but no recurrence was found in the previously affected breast. It was interesting to note that though she had never menstruated the girl had a fairly profuse bleeding about ten days after the treatment was over. Her mother, however, had been warned of this

but in 2 secretion persisted; in 2 there was a recurrence of lactation later and 2 had painful breasts. Two had mastitis, but in 1 it was present before the treatment was adopted.* In all, 113 cases (Table II) were treated with complete inhibition in 104

TABLE II

Inhibition of Lactation

	Drug.	Method of Use	Dosage.		Number of Cases.	Response.				
			Total (mgm.).	Daily (mgm.)		Complete Inhibition of Lactation.	Persistent Secretory Activity.	Recurrence of Secretion	Engorged or Painful Breasts.	Infection.
I	Triphenyl chloroethylene	Injection in oil	250-300	..	55	52	3	...	6	3
II	" " "	Injection of "dispersion" in water	250	.	14	14	.	..	..	2
III	" " "	Orally	3800-4800	1 1500 2 1500 3 600-800 4 200-800	11	11	.	...	1	1
IV	Triphenyl methylethylene	Orally	450	1 150 2 150 3 100 4 50	7	5	2	...	.	...
V	Diethyl-stilboestrol	Orally	45	1 15 2 15 3 10 4 5	26	22	2	2	2	2
	..				113	104	7	2	9	8

No toxic side actions occurred in any of the cases

cases or 92 per cent. *No toxic side actions occurred in any of the cases*, and there was no persistence of red discharge, and no early return or later irregularity of the menses noted. T.P.E. by injection is most useful when a stillbirth occurs, as the injection

* In private practice I have used slightly larger doses of ovendosyn or ... gm thrice daily for 3 days, twice daily for ... thout any toxic side actions except for one ... the results have been most satisfactory

THE USES AND ABUSES OF THE FEMALE SEX HORMONES

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It would be an overwhelming task to cover in one lecture the whole field of therapeutics of the female sex hormones and, at the same time, present in any dogmatic form the indications for their clinical application. Our knowledge of female sex endocrinology is as yet far from complete, and this fact probably explains the many conflicting clinical results found in the extensive literature on this subject. Scientific and clinical research has, however, progressed so far that in certain conditions it is now possible to prescribe sex hormone preparations with the sure knowledge that they are effective and curative therapeutic agents. On the other hand, unless one has some understanding of the functions of the endocrine secretions, there is the ever-present danger of the indiscriminate use of these preparations. As a result they may not only prove ineffective but on occasion they may be contra-indicated, particularly in cases in which there has been insufficient primary investigation. Whilst realising the many pitfalls, I shall endeavour to place before you a balanced synthesis of the facts as at present known in regard to the application of the therapeutic preparations at our disposal

The hormones most closely related to female sex physiology are the gonadotrophic hormone secreted by the anterior pituitary gland, œstradiol elaborated by the developing Graafian follicles of the ovary, and progesterone secreted by the corpus luteum.

Anterior Pituitary Gonadotrophic Hormone

The anterior pituitary gland through its gonadotrophic hormone controls the development of the Graafian follicle, ovulation and corpus luteum formation. At the present time

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possibility, and therefore they were not alarmed. A few months later another girl, aged fifteen, was sent to me with a somewhat similar condition in both breasts, which had caused most agonising pain for some weeks and had resisted all palliative treatments. She was similarly treated and progressed favourably whilst under treatment, but she had several recurrences owing to the utmost difficulty in getting her to carry on or attend for treatment after the pain had subsided.

Premenstrual mastalgia can also sometimes be benefited by small doses of œstrogen for two to three days before the pain is expected.

From this personal and therefore far from complete account it would appear that œstrogenic therapy can be of the greatest value for many conditions when it is used with discretion, and it is hoped that with future chemical and clinical research its sphere of action will be still further expanded.

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By Assistant Gynæco- Consultant Obstetrician, Northern Counties of Scotland; Hon. Gynæcologist, Royal Northern Infirmary, Inverness.

It would be an overwhelming task to cover in one lecture the whole field of therapeutics of the female sex hormones and, at the same time, present in any dogmatic form the indications for their clinical application Our knowledge of female sex endocrinology is as yet far from complete, and this fact probably explains the many conflicting clinical results found in the extensive literature on this subject. Scientific and clinical research has, however, progressed so far that in certain conditions it is now possible to prescribe sex hormone preparations with the sure knowledge that they are effective and curative therapeutic agents. On the other hand, unless one has some understanding of the functions of the endocrine secretions, there is the ever-present danger of the indiscriminate use of these preparations. As a result they may not only prove ineffective but on occasion they may be contra-indicated, particularly in cases in which there has been insufficient primary investigation. Whilst realising the many pitfalls, I shall endeavour to place before you a balanced synthesis of the facts as at present known in regard to the application of the therapeutic preparations at our disposal.

The hormones most closely related to female sex physiology are the gonadotrophic hormone secreted by the anterior pituitary gland, œstradiol elaborated by the developing Graafian follicles of the ovary, and progesterone secreted by the corpus luteum.

Anterior Pituitary Gonadotrophic Hormone

The anterior pituitary gland through its gonadotrophic hormone controls the development of the Graafian follicle, ovulation and corpus luteum formation. At the present time

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there is no reliable anterior pituitary preparation available for use which can simulate the actions of the naturally occurring gonadotrophic hormone; there are, however, two preparations which are of considerable therapeutic value, namely, serum gonadotrophic hormone prepared from pregnant mare's serum, and urine or chorionic gonadotrophic hormone extracted from pregnancy urine. The former stimulates follicular development; the latter causes corpus luteum formation. A combination of these two preparations forms a useful therapeutic agent indicated in conditions directly or indirectly associated with defective action of the anterior pituitary gland.

The Ovarian Hormones

The ovarian hormones are œstradiol or œstrogenic hormone elaborated by the developing Graafian follicles, and progesterone secreted by the corpus luteum. The corpus luteum not only elaborates its specific hormone, progesterone, but it also secretes œstradiol. Progesterone and œstradiol are the true or naturally occurring hormones of the ovaries and are produced for the most part by the ovaries under the stimulus of the gonadotrophic hormone of the anterior pituitary; they are also secreted in variable amounts by other internal secretory glands, such as the adrenals Potent preparations of these hormones have been available for some time. The elucidation of their chemical formulæ gave rise to an intensive chemical investigation of their properties. Now as a result of the researches of Dodds and his co-workers (Dodds, 1934, Dodds *et al*, 1938; Campbell *et al.*, 1939), and of Robson and Schönberg, 1937, we have available for clinical use synthetic preparations of œstrogenic hormone, such as diethyl stilbœstrol, hexœstrol and triphenylchloroethylene, which, though not chemically related, simulate closely the actions of the naturally occurring hormones (Bishop *et al.*, 1939, Winterton and MacGregor, 1939; MacPherson and Robertson, 1939) They have the added advantage of being active when given orally.

The uncontrolled production of synthetic œstrogens, each with a trade name, has had the advantage of their being readily available at little cost to the patient, but it is believed that this advantage is to a considerable extent outweighed by the tendency at the present time to utilise them in conditions in which they would seem to be harmful or even contra-indicated.

Anhydro-oxy-progesterone is a synthetic preparation of progesterone which is also active when given by mouth, but the effective dosage given orally is six times that given by injection.

The uses of the sex hormones may conveniently be considered in two groups: Gynæcological Disorders and Obstetrical Conditions. Their use in general endocrine and constitutional disturbances will only be referred to in so far as they are related to these conditions.

GYNÆCOLOGICAL DISORDERS

(A) Before Puberty

As the sex glands only assume full function at puberty, there are thus few indications for the use of the sex hormones before this time. There is one condition, however, namely, vulvo-vaginitis, which can be effectively treated by œstrogenic hormone in the form of vaginal pessaries or by oral administration. The œstrogens stimulate the growth of the vaginal epithelium, and with the resulting increased glycogen content of the cells, additional lactic acid is available so that not only is the infection controlled by the shedding of the epithelial squames, but the increased acidity of the vaginal flora proves inimical to the causative organism.

It should be noted that the sulphonamides, especially sulphathiazol and sulphadiazine, are also effective in this condition and have none of the minor disadvantages, such as enlargement of the breasts, which are sometimes also associated with the administration of the œstrogens.

(B) During the Period of Reproductive Life

(1) *Disturbances of Menstrual Rhythm*

(*a*) *Metropathia Hæmorrhagica.*—The most common cause of irregular uterine bleeding is metropathia hæmorrhagica or cystic glandular hyperplasia. This condition may occur at any time, but is more common at the beginning and end of the period of reproductive life. It is characterised by a long intermenstrual period, five to ten weeks, followed by excessive and prolonged menstrual loss. It is possible that a minor psychological disturbance, acting through the higher cerebral centres

and interfering with anterior pituitary function, forms the predominant etiological factor in metropathia hæmorrhagica. The essential cause of the condition, however, is a failure of ovulation with concomitant excessive production of the œstrogenic hormone. Failure of ovulation must be due to (*a*) the provision of an inadequate anterior pituitary stimulus to the ovary, or (*b*) some inherent defect in the ovary, such as a partially thickened tunica albuginea, or diminished reactivity—contingencies which may be expected to occur towards the end of the life span of the ovary. The hormonal imbalance, once established, may persist for a considerable time before it returns to normal, but during that time generally the sequelæ of glandular dysfunction, such as excessive blood loss, make active and appropriate therapy imperative.

A consideration of the salient features of metropathia hæmorrhagica suggests that a rational form of therapy is the administration of an anterior pituitary preparation which would cause full maturation of the Graafian follicle, ovulation, and corpus luteum formation. It is not likely, however, that anterior pituitary therapy could have any effect on cysts already developed in the ovary. It is those cysts which are responsible for the continuous outpouring of œstrogenic hormone into the bloodstream. The resulting high concentration of œstrogenic hormone in the blood further impairs by inhibition the defectively functioning anterior pituitary. The mobilisation of the corpus luteum hormone, however, antagonises this excessive production or increased blood concentration of the œstrogenic hormone. As a direct consequence of this, there is release of the inhibition of the anterior pituitary gland or its gonadotrophic hormone and thus a normal hypophyseal-ovarian relationship is established

Serum gonadotrophic hormone, which simulates most closely the true hypophyseal hormone, has been used in this condition with promising results (Kenny and Daley, 1941). In adolescence urine or chorionic gonadotrophic hormone is sometimes found to be effective in controlling irregular bleeding (Fluhmann, 1939). At this time the ovaries are probably more receptive to stimulation. The effect produced is likely to be luteinisation of the developing or partially developed follicles, which then secrete progesterone.

Administration of the corpus luteum hormone in these cases is also an effective form of therapy (MacGregor, 1938). It has a threefold effect: (*a*) it controls the bleeding in virtue of its action on the uterine endometrium, (*b*) it counteracts the excessive

blood concentration of the œstrogenic hormone, and thus releases the inhibition of the anterior pituitary—the œstrogenic hormone in excess inhibits the gonadotrophic hormone of the anterior pituitary; (*c*) it tides the patient over a period of endocrine imbalance until the anterior pituitary can fully function. A similar effect may be obtained with male hormone, but its use may be associated with rather disturbing side-effects, such as hirsutism, and accordingly it is probably not advisable in the early years of womanhood.

In the present state of our knowledge progesterone seems to be the most effective therapy for metropathia hæmorrhagica and, pending more potent anterior pituitary preparations, it is the one most likely to meet with success, but the dosage must be adequate and the treatment must be energetic if satisfactory results are to be obtained. The intramuscular injection of 5 to 10 mgs. of progesterone daily until the bleeding is controlled has been found to be an effective dosage (MacGregor, 1938).

The rôle of the œstrogenic hormone in functional uterine bleeding has recently been investigated, and not unfavourable results have been reported (Karnaky, 1940; Palmer, 1941; Culyer *et al.*, 1942). The results obtained in cases of irregular uterine bleeding treated by œstrogenic hormone, and later referred to me, have been uniformly unsatisfactory. Recognition of the hormonal disturbance which operates in cases of abnormal uterine bleeding associated with failure of ovulation suggests that œstrogenic hormone therapy rather than being beneficial is more likely to be harmful, as in such cases the bleeding is due to a high concentration of œstrogenic hormone in the blood, and it seems illogical to increase the blood concentration of the hormone by administration of more œstrogen. Admittedly, the œstrogens are inexpensive and can be readily obtained, but it must be emphasised that they are potent therapeutic agents and as such have to be used with caution The following case record illustrates how the œstrogens may be abused or at least misapplied.

Mrs D., aged 41. Para 3. First seen 28th April 1943, when the following history was obtained: Menses regular 5/35 until three years ago, when the rhythm became 10/24. In October 1942 she began to have very severe floodings with her periods and was treated with ergot and intramuscular pituitary. When seen she had had more or less continuous bleeding for the previous two months. On going further into her history it was

found that she had been taking 1 mg. stilbœstrol dipropionate t.i.d. almost continuously for one year. On examination it was found that the cervix was patulous, the uterus was retroverted and considerably enlarged. Curettage of the uterus revealed a profuse and polypoidal endometrium, the histological examination of which showed a very characteristic picture of metropathia hæmorrhagica.

The œstrogenic hormone in this case had been given with a view to controlling the excessive menstrual loss, but with no effect; in fact, its continued administration provoked increased menstrual loss with concomitant constitutional debility.

(*b*) *Ovular Bleeding, Hypomenorrhœa and Oligomenorrhœa.*—These are *minor disturbances of the menstrual rhythm.* Ovular bleeding, as the term implies, is the bleeding which is sometimes associated with ovulation. It is believed to be due to a transient diminution of the œstrogenic hormone concentration occurring between the time of ovulation and mobilisation of the corpus luteum (MacGregor, 1938). The temporary drop in the amount of circulating œstrogenic hormone results in a diminished stimulation of the uterine endometrium, which partially breaks down and causes bleeding In some the bleeding may be very slight and represented by only a few spots, whilst in others the amount of blood lost may be similar to that of the normal period Owing to the danger of inhibiting directly the anterior pituitary and indirectly ovulation, œstrogenic hormone is contra-indicated in this condition. The stimulation of the endometrium can, however, be adequately maintained in such cases by giving 5 mgs. progesterone intramuscularly the day before the expected bleeding and for two days thereafter. A course of therapy over three menstrual cycles is usually efficacious.

Hypomenorrhœa, or scanty menstrual loss, is not common and in most cases it is of no serious significance, as in such cases there is usually no failure of ovulation There are a few cases, nevertheless, in which there is failure of ovulation, and in such the bleeding is associated with the proliferative phase of the endometrium—so-called anovular menstruation. The importance of this type of menstruation in sterility is evident. An effective therapy must promote follicular maturation and ovulation; this can only be done by administration of anterior pituitary hormone, particularly the serum gonadotrophic hormone, given in doses of 200 international units every third day for five injections, starting at the onset of the menstrual period.

Oligomenorrhœa, or delayed menstruation, is not uncommon. It is a frequent precursor of functional amenorrhœa and is prone to occur at the beginning and end of the period of reproductive life. Towards the menopause the bleeding is frequently associated with a proliferative endometrium, but at other times for the most part it is associated with a secretory endometrium. Thus there is a long proliferative phase of the endometrium and a normal secretory phase. The therapy indicated is one which will accelerate follicular development and ovulation; accordingly, the treatment most likely to be effective is the administration of anterior pituitary in the form of serum gonadotrophic hormone (200 i.u.) alone or in combination with urine gonadotrophic hormone (100 i.u.) every third day for five injections at the onset of the period. These preparations should be given over three menstrual cycles at the time corresponding to the pre-ovulatory phase.

(2) *Dysmenorrhœa*

There are few women who do not have some discomfort at the menses, but in the majority of cases the discomfort is so slight that attention to normal functions and the use of mild analgesics is effective. Others, however, are incapacitated by the menstrual pain and discomfort. In some a pathological condition of the uterus or uterine adnexa is the causative factor, the treatment of which only can bring relief. There are many cases, however, in which no obvious pathology exists and, although there may be a psychological basis for the pain, hormone therapy is frequently efficacious. It is reasonable to assume that the rhythmic interplay of the ovarian secretions, which exert their influence on the uterus and uterine adnexa, may be maladjusted and increased function of one partially override the function of the other. It is known that the œstrogenic hormone sensitises the uterine musculature, promotes the proliferative phase of the endometrium and increases the vascularity of the pelvic structures; whereas progesterone inhibits uterine activity and stimulates the secretory phase of the endometrium. The important point to keep in mind, however, is that the corpus luteum secretes both hormones and that they act synergistically on the uterus. Primary dysmenorrhœa, in my experience, is invariably associated with ovulation; women who do not ovulate do not have painful periods (Wilson and Kurzrok, 1938; Sturgis and Albright, 1940). This is clearly

demonstrated in cases of ovular bleeding, œstrin-withdrawal bleeding and the bleeding associated with metropathia hæmorrhagica. In these cases there is unopposed œstrogenic action, and consequently there is no pain associated with the bleeding. Painful menstruation is not necessarily associated with uterine hypoplasia or hyperplasia *per se.*

As a result of clinical investigation, one believes that it is only when there is a deviation from the normal finely adjusted concentration of the two ovarian hormones that the uterine reactivity becomes disordered, giving rise to pain either before or during menstruation. If this contention is correct, then hormone therapy for the relief of dysmenorrhœa should only be given during the second half of the menstrual cycle. Premenstrual dysmenorrhœa, in the absence of pelvic pathology, is most frequently associated with excessive œstrogen or deficient progesterone production, and can be controlled by progesterone therapy in doses of 5 mgs. every second day, starting eight days before the expected period. Conversely, menstrual dysmenorrhœa may be associated with excessive progesterone or subnormal œstrogenic hormone secretion, and can be relieved by the administration of œstrogenic hormone in doses of 5 mgs. of synthetic preparation given thrice daily for four days prior to the onset of the period. The œstrogenic hormone is frequently administered during the first half of the menstrual cycle in cases of dysmenorrhœa, and this form of therapy may be temporarily effective, but it acts by suppressing ovulation (Sturgis and Albright, 1940), and consequently there is always the danger of producing an abnormal condition, the treatment of which may be much more difficult than that of the primary disturbance.

(3) *Sterility*

It is important to understand the rôle of the female sex hormones in the treatment of sterility, as they are frequently misused in this condition Now, if ovulation takes place, corpus luteum formation follows normally—this is confirmed if one obtains a typical secretory endometrial pattern in the tissue removed with the biopsy curette immediately before a period, or if pregnandiol can be recovered from the urine in the post-ovulatory phase—and there would therefore appear to be no indication for hormone therapy If repeated examinations—and one examination is not conclusive—show that ovulation is

not occurring, then an anterior pituitary preparation to stimulate ovulation is indicated. It has been shown that anterior pituitary preparations, especially serum gonadotrophic hormone, can promote ovulation (Davis and Koff, 1938; Griffith and McBride, 1942). Green-Armytage (1943) contends that small doses of œstrogen, for example, ½ to 1 mg. hexœstrol, given daily during the first five days of the cycle, that is during menstruation, have a beneficial effect not only on the *p*H of the vaginal secretion, but also promote a healthier condition of the mucous plug—conditions favourable to the spermatozoa. There is also convincing evidence that administration of the œstrogens promotes canalisation of the Fallopian tubes in proved cases of tubal occlusion (Clauberg, 1938; Moore White, 1940). These causes of sterility are found only after thorough investigation, and the œstrogens are given in order to evoke a definite and known response. The danger of œstrogenic therapy in sterility, however, is that of so depressing pituitary function as to inhibit ovulation, thus preventing the occurrence of conception and promoting a pregnancy complex.

The following case record indicates the danger of unwarranted œstrogenic hormone therapy in sterility:

Mrs A., aged 25. Para 0. First seen 14th April 1943, when the following history was obtained. On 20th January 1943 a curettage was carried out on account of sterility. Normal period started on 5th February, and immediately period was over the patient was put on stilbœstrol 1 tablet t.i.d (dose not given on prescription) for fourteen days. On 3rd March she had a brownish discharge which lasted two days and which appeared again after two days associated with pain in the left lower quadrant of the abdomen. On 10th April the brownish discharge became bright red and continued until patient was seen on 14th April. There was no history of sickness, but a feeling of engorgement of the breasts and frequency of micturition. On examination the uterus was in good position, not enlarged, but unduly sensitive. No palpable abnormality could be detected in the right appendages, but in the left side a small tender swelling could be palpated. A tentative diagnosis of an unruptured ectopic gestation was made, and as the patient lived at a considerable distance from hospital facilities it was decided to operate.

At operation there was no evidence of an ectopic gestation, but the left ovary was enlarged to the size of a large plum and

adherent to the posterior layer of the broad ligament. The uterus was curetted to exclude any question of an intra-uterine pregnancy, and histological examination of the uterine scrapings disclosed an endometrium in the proliferative phase.

(4) *Amenorrhœa*

Although amenorrhœa is due in most cases to a physiological or a pathological condition, there is, nevertheless, a large number of cases in which no cause for the amenorrhœa is apparent. A study of the history in such cases, however, leads one to the conclusion that in the majority there is an exciting psychological disturbance (MacGregor, 1938); in some it is trivial, whilst in others it may be grave. It is known that the suppression of menstrual function may persist for varying periods after the readjustment of the psychogenic disturbance and may be permanent unless endocrine therapy is instituted. The effect of psychological trauma on the menstrual cycle is frequently seen, at the present time, in girls serving in His Majesty's Forces. After joining the Services it is not unusual for some girls to have amenorrhœa for periods varying from three to nine months, menstruation only returning spontaneously some considerable time after they have adjusted themselves to their new mode of life. Although the spontaneous onset of the menses in secondary amenorrhœa may be expected up to a period of one year, it is not advisable that treatment should be delayed beyond this time. The longer the period of amenorrhœa the more difficult it is to re-establish a normal menstrual cycle.

When potent preparations of the ovarian hormones became available the outlook in the treatment of amenorrhœa appeared promising, but the results obtained have not fulfilled the earlier expectations of this form of therapy. There may be several reasons for this, the most important of which are:—

(1) The failure to realise that the ovarian hormones can play only a limited rôle in the treatment of amenorrhœa. Administration of the œstrogenic hormone stimulates the growth of the uterine endometrium and muscle, as in many cases of long-standing amenorrhœa both have become hypoplastic (MacGregor, 1936). The stimulation of the uterus to full development is the predominant indication for the use of the œstrogens in this condition. The uterine bleeding which follows after the cessation of the treatment—and several courses of therapy may be required

to produce this result—may be taken as evidence that this effect has been produced and therefore there is no further indication for ovarian therapy. The shorter the period of amenorrhœa the more readily is this result to be anticipated. The psychological effect of the appearance of vaginal bleeding in some susceptible individuals is occasionally beneficial and may be associated with the return of a normal menstrual cycle.

It has been shown that bleeding can be induced in amenorrhœic women by the administration of progesterone given in large doses over a short interval of time (Zondek, 1942). The induction of a pseudo-menstruation by this form of therapy, however, is followed by a return to the normal cycle in only a few cases, especially in those cases where the amenorrhœa is of short duration—cases in which menstruation would probably have returned spontaneously.

(2) The introduction of endocrine treatment for amenorrhœa without excluding pathological causes such as tuberculous endometritis (MacGregor, 1936).

(3) The tendency to overlook the fact that psychological trauma may be followed by serious constitutional sequelæ of which amenorrhœa may be only a minor manifestation. It seems unwise to concentrate on the treatment of amenorrhœa associated with anorexia nervosa without initially treating the constitutional disturbance; similarly, amenorrhœa is, in many cases, associated with obesity, and it is found that a more favourable outcome may be anticipated when the treatment is directed in the first place towards counteracting the obesity (MacGregor, 1938).

Ovarian function in the majority of cases of functional amenorrhœa is minimal or in abeyance as a direct result of defective anterior pituitary stimulation. Although the œstrogens are effective in sensitising the uterus to the normal ovarian stimulus—and this is considered to be a necessary preliminary therapy—the essential treatment is the administration of an anterior pituitary preparation in order to stimulate the ovaries to full function and hormone production (MacGregor, 1938; Rydberg and Pedersen-Bjergaard, 1943). This, of course, is substitutional treatment, but differs from ovarian therapy in that it supplies or supplements the impetus necessary to set in motion the whole endocrine mechanism of which the ovaries form only one part. It is known that there is a reciprocal interaction between the secretions of the hypophysis and ovaries; for example,

the anterior pituitary stimulates production of the ovarian hormones, but when they reach a certain concentration in the blood they begin to have an inhibitory action on the anterior pituitary gland. Moreover, the hypophysis controls the hormone production of the other glands in the endocrine chain. Now the promotion by anterior pituitary therapy of ovarian hormone production at a normal level, I believe, not only restores the general endocrine balance, but the adjusted interplay of all the endocrine secretions may also react beneficially on the anterior pituitary.

(5) *The Menopause*

Towards the end of the reproductive period women evince varying reactions towards this important epoch in their lives; some are assailed and even tormented with fears, doubts and forebodings of what the future holds for them, whilst others who may have striven to bear and bring up a large family look forward to this time with cheerful anticipation. It is not surprising, therefore, that some women have an unhappy and trying time at this period whilst others pass through it with little or no discomfort The endocrine system which normally adjusts itself when ovarian function ceases, is most probably affected by the mental status of the individual. An important factor in the production of an unfavourable mental reaction is the fear of loss of sexual function—many women believe that sexual life ceases at the menopause—and the allaying of this dread may frequently change the whole outlook.

The menses may cease abruptly in some women, but in the majority the change is a slow process and may be associated with menstrual irregularity Frequently there is a regular sequence in the menstrual cycle which may be considered normal, such as a period once every two or three months with normal or scanty loss. If, however, there is uterine bleeding after an interval of four months, it should be regarded as indicative of an abnormal condition. Carcinoma of the uterus is so frequent at the climacteric that it must be excluded by a thorough pelvic examination and curettage of the uterus in every case of abnormal uterine bleeding occurring at this time. Apart from neoplastic conditions of the uterus, irregular uterine bleeding at the menopause is frequently associated with failure of ovulation. The value of progesterone therapy in this type of bleeding has already been discussed, but some cases at the climacteric prove resistant to this form of

treatment as the ovary at the end of its life-span does not always react normally to the anterior pituitary stimulus released by the administration of progesterone. In these cases the menopause may have to be induced surgically or by radium or X-ray therapy. There appears to be no indication for the use of the œstrogens in irregular bleeding occurring at the menopause, for the reason that the bleeding may be associated with an already excessive secretion of the hormone and any effect can only be of a very temporary nature. It should be emphasised that slight irregular uterine bleeding in women at the menopause may be symptomatic of a pathological process, and the administration of œstrogenic hormone in these cases, though it may temporarily arrest the hæmorrhage, merely masks the serious condition and delays, not without danger, operative or other appropriate treatment. It is astonishing, however, how frequently the œstrogens are abused in the treatment of women complaining of menstrual irregularities at the climacteric.

A consideration of the amounts of œstrogenic hormone required to control the subjective phenomena characteristically noted after the cessation of menstruation and of the concentration of the hormone required to initiate uterine bleeding, strongly suggests that if menstruation has not ceased or is irregular, there is present a sufficiency of the hormone in the blood to counteract any symptoms such as insomnia, flushes, irritability, etc., and that some other cause must be found for these symptoms. Symptoms such as these may be indicative of early organic disease. The slightest deviation from the normal in the menstrual rhythm and any and every untoward symptom arising in a woman nearing the change of life are, in my opinion, erroneously being made an indication for œstrogenic hormone therapy. Moreover, the synthetic œstrogens are advertised widely in women's journals—they can be obtained without a doctor's prescription—as being effective not only for the relief of distressing symptoms but also for menstrual irregularities It is impossible to estimate the harm which may be done by the indiscriminate use of these preparations, especially if the symptoms are indicative of an incipient organic disease or the menstrual irregularity is symptomatic of an early malignant condition

The œstrogens are pre-eminently effective in controlling the subjective symptoms associated with the cessation of ovarian function. The hot flushes, irritability, depression, etc , which are so common and which, as already pointed out, are conditioned

to a certain extent by the psychological status of the individual, can be completely relieved by œstrogenic hormone therapy. It is known that there is a marked over-activity of the anterior pituitary at the menopause, as is evidenced by the excessive urinary excretion of gonadotrophic hormone (Zondek, 1931). The inhibition of the anterior pituitary, however, is only temporary, as excessive amounts of gonadotrophic hormone may be found in the urine in women many years past the menopause who have no symptoms (Jones and MacGregor, 1936). Such findings suggest that the inhibition of the anterior pituitary with the œstrogens is only a temporary expedient which permits the endocrine system to adjust itself to the absence of the ovarian secretions. Moreover, the more effectively the hypophysis is inhibited initially with complete relief of symptoms, the more quickly is the adjustment likely to follow. For this reason a high dosage of the œstrogens, such as 5 mgs. synthetic œstrogen thrice daily, should be given until all symptoms are relieved, and then the dosage should be gradually diminished over a period of six to eight weeks. Satisfactory results have been obtained in the artificially induced menopause by the administration of small doses of the œstrogens given as a prophylactic measure before any untoward symptoms arise (Haultain, 1942).

It is important to recognise that occasionally the menopausal phase may pass imperceptibly into the abnormal and that some patients, complaining initially of mild depression, may become definitely psychotic. The œstrogens are of value in such cases when used as an adjuvant to general psychiatric treatment (Jones *et al.*, 1937).

(C) Post-Menopause

During the period of reproductive life the œstrogenic hormone maintains the development and tonicity of the secondary sex organs and external genitalia The essential change which takes place in the genital tract after the menopause is one of atrophy and loss of tonicity of the tissues The uterus becomes hypoplastic, the vaginal walls become thinner and the vulva loses its resiliency. At this time, therefore, any infection of the reproductive tract, specific or non-specific, meets with little or no resistance. Conditions such as senile vaginitis, kraurosis vulvæ and leucoplakia vulvæ, are associated with infections of the genital tract occurring after the menopause. In cases of senile vaginitis and kraurosis vulvæ the restoration of the tissues, by the administra-

tion of œstrogenic hormone, to the same state of development as that found during reproductive life, supplies the necessary resistance to overcome the infection. There is increased vascularity of the tissues and regeneration of the epithelium, and, in senile vaginitis, the change in the vaginal flora makes it inimical to the causative organism (Davis, 1935; MacGregor, 1938). Leucoplakia vulvæ, if treated in the early phase, responds satisfactorily to this treatment but may prove refractory in the later stages. The dosage of the œstrogens employed in these conditions should be a large one, say 15 mgs. daily, administered over a short period.

The administration of the œstrogens to elderly women subsequent to operation for genital prolapse promotes the vascularity and regeneration of the tissues, which ensure sound healing. This therapy proves particularly beneficial in those cases in which the vaginal tissues are unduly friable and atrophic.

Pruritus vulvæ is not uncommon after the menopause, and in the majority of cases a specific etiological factor can be ascertained. There are some cases, however, in which no cause can be found, and in these the condition may be associated with some irritative lesion of the nerve endings arising from the atrophy of the tissues. Œstrogenic hormone therapy is often eminently successful in these resistant and difficult cases. It may be necessary to give a very high dosage if no result is obtained with a moderate dose. It should be noted, however, that it is not advisable to give a high dosage over more than a short interval of time. One case treated eighteen months ago did not react favourably until a dosage of 45 mgs. of synthetic œstrogen was given daily for seven days. The pruritus was completely relieved This high dosage of œstrogen, however, provoked such a marked hypertrophy of the vaginal epithelium as to form a plaque in the anterior wall. Cystoscopic examination suggested a malignant condition of the base of the bladder, but the vaginal mucosa eventually returned to its normal post-menopausal state The patient remained free of irritation until a recurrence two weeks ago.

The most common etiological factor responsible for post-menopausal bleeding is a malignant condition of the uterus or its adnexa The incidence of malignant disease is so high that it should be immediately excluded by curettage of the uterus in every case of post-menopausal bleeding, no matter how slight the bleeding, and irrespective of the fact that there may be a benign condition present to account for it. It cannot be

to a certain extent by the psychological status of the individual, can be completely relieved by œstrogenic hormone therapy. It is known that there is a marked over-activity of the anterior pituitary at the menopause, as is evidenced by the excessive urinary excretion of gonadotrophic hormone (Zondek, 1931). The inhibition of the anterior pituitary, however, is only temporary, as excessive amounts of gonadotrophic hormone may be found in the urine in women many years past the menopause who have no symptoms (Jones and MacGregor, 1936). Such findings suggest that the inhibition of the anterior pituitary with the œstrogens is only a temporary expedient which permits the endocrine system to adjust itself to the absence of the ovarian secretions. Moreover, the more effectively the hypophysis is inhibited initially with complete relief of symptoms, the more quickly is the adjustment likely to follow. For this reason a high dosage of the œstrogens, such as 5 mgs. synthetic œstrogen thrice daily, should be given until all symptoms are relieved, and then the dosage should be gradually diminished over a period of six to eight weeks. Satisfactory results have been obtained in the artificially induced menopause by the administration of small doses of the œstrogens given as a prophylactic measure before any untoward symptoms arise (Haultain, 1942).

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place at the third month. A lag in the change over, resulting in a lowering of the progesterone threshold, would furnish an explanation of the frequency of abortion at this time (MacGregor and Stewart, 1939). The administration of progesterone in large doses (10 to 20 mgs. daily) at the very earliest stage of a threatened miscarriage is frequently effective in saving the pregnancy. If much placental separation has occurred, however, the abortion will become inevitable and progesterone therapy is then valueless. It should be noted that progesterone therapy alone in threatened miscarriage is not enough; rest must be enforced and anxiety allayed by the use of sedatives.

(3) *Recurrent Abortion.*—The administration of progesterone early in pregnancy has resulted in the continuation of the pregnancy to term in many cases of recurrent abortion (Kane, 1936; Bishop, 1937; Elden, 1938; MacGregor and Stewart, 1939). An adequate dosage, such as 5 to 10 mgs. twice weekly, must be given as soon as the pregnancy is diagnosed and continued until at least the end of the fourth month of pregnancy. It is advisable to supplement this therapy by the administration of vitamin E.

The œstrogens, in virtue of their function of increasing the sensitivity of the uterine muscle, have been used in (*a*) missed abortion, (*b*) induction of labour, and (*c*) uterine inertia.

(*a*) *Missed Abortion.*—As is well known, a dead ovum may be retained *in utero* for intervals of time varying from weeks to months. The cause of the retention of the ovum is presumably the diminished sensitivity of the uterine muscle This can be overcome by the administration of œstrogens, and this form of therapy is frequently very successful in missed abortion and premature death of the fœtus (Jeffcoate, 1940, Haultain, 1942). As the œstrogens are fairly rapidly destroyed in the body, it is suggested that a high dosage should be given over a short interval of time. I have obtained satisfactory results with 10 mgs of synthetic œstrogen given hourly for six to ten hours, supplemented in some cases by posterior pituitary extract. This high dosage is well tolerated The more advanced the pregnancy the more successful is this form of treatment.

(*b*) *Induction of Labour and Premature Death of Fœtus.*—When given alone the œstrogens are rarely effective in inducing labour, but when employed as part of a scheme of induction they may be of value, although their usefulness in these cases is difficult to assess. They are, however, efficacious in the induction

emphasised too strongly that post-menopausal bleeding, *per se*, is never an indication for œstrogenic hormone therapy, yet one frequently finds it being given quite unjustifiably in this condition.

Some women may have an uneventful climacteric but complain of subjective symptoms late in life similar to those experienced at the menopause. Such cases can be effectively treated with the œstrogens, but they usually require a small maintenance dose given over a prolonged period.

OBSTETRICAL CONDITIONS

The corpus luteum hormone or progesterone has well-defined physiological actions in the initiation and continuation of pregnancy. It is responsible for the decidual reaction of the uterine endometrium, thus preparing the endometrium for the nidation of the fertilised ovum. Its sedative action on the uterine musculature promotes conditions favourable for the process of embedding of the ovum and the early development of the placenta, and its uninterrupted production is essential for the continuation of the pregnancy. Consideration of these facts suggests the usefulness of progesterone therapy in (1) repeated early miscarriage suspected when the period is a few days late, (2) threatened abortion, and (3) recurrent abortion.

(1) *Early Miscarriage*.—This frequently occurs without the patient's knowledge, or it may be suspected when the period is repeatedly but not continuously a few days late. Some women realise intuitively that conception has occurred. A continuation of the pregnancy in such cases can be brought about by the administration of progesterone, 5 to 10 mgs. twice weekly, begun during the second half of the menstrual cycle and continued until at least the fourth month is reached.

(2) *Threatened Abortion*.—Abortion most frequently occurs at the time of the suppressed period, and it reaches its highest incidence at the time of the third missed period. The explanation for the frequency of abortion at the third month is not clear. The placenta, by the time this stage is reached, is fully developed. It is known that pregnancy can continue when the corpus luteum of pregnancy is removed at an early stage (Jones and Weil, 1938). The assumption is, therefore, that the placenta secretes the necessary amount of progesterone required for the continuation of the pregnancy. The change over from corpus luteum to placental production of progesterone probably takes

place at the third month. A lag in the change over, resulting in a lowering of the progesterone threshold, would furnish an explanation of the frequency of abortion at this time (MacGregor and Stewart, 1939). The administration of progesterone in large doses (10 to 20 mgs. daily) at the very earliest stage of a threatened miscarriage is frequently effective in saving the pregnancy. If much placental separation has occurred, however, the abortion will become inevitable and progesterone therapy is then valueless. It should be noted that progesterone therapy alone in threatened miscarriage is not enough; rest must be enforced and anxiety allayed by the use of sedatives.

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of labour in cases where the fœtus dies *in utero* near term, and also in some cases of premature rupture of the membranes associated with delay in the onset of labour.

(*c*) *Uterine Inertia.*—The œstrogens have been found to be effective in more than half of a series of cases of uterine inertia (Jeffcoate, 1938). In my experience the results of this form of therapy have been inconclusive, as it has not been found possible to induce increased uterine sensitivity in many cases in which the indications for its use appeared to be specific and in which a satisfactory response was anticipated.

Suppression of Lactation

The development of the breasts during pregnancy in preparation for lactation is brought about by the actions of the œstrogenic and corpus luteum hormone. The secretion of milk in the breasts on the third or fourth day of the puerperium is due to prolactin or mammotrophic hormone of the anterior pituitary gland, whilst the continuation of milk production is associated with the stimuli arising from the act of suckling. During pregnancy and for the first two or three days of the puerperium the mammotrophic hormone of the anterior pituitary is probably inhibited by the high blood concentration of the œstrogenic hormone; the delivery of the placenta results in the release of this inhibition. The administration of œstrogens, however, either before or after lactation is established, can again bring about the inhibition of the anterior pituitary milk-secreting hormone; the breast either does not secrete milk or its secretion quickly subsides with this therapy, provided suckling does not take place. As the administration of œstrogens to a nursing mother does not inhibit the secretion of milk, it would seem that the reflex act of suckling must stimulate the increased secretion of prolactin (Abarbanel and Klein, 1941; Stewart and Pratt, 1941). The important part played by the act of suckling in hormone production, leading to milk secretion, suggests how readily the endocrine system is influenced by nervous stimuli.

In cases where breast feeding is contra-indicated, œstrogen therapy should be started the day after delivery It is advisable to give an effective dose initially—5 mgs. thrice daily for four days, followed by 5 mgs daily for six days is usually effective—in order to produce complete inhibition of the lactogenic hormone. Lactation can be inhibited in every case provided the dosage is

adequate; the puerperal patient can tolerate a high dosage of œstrogenic hormone.

In the preceding pages I have assayed to interpret the rôle of the sex hormones in certain gynæcological and obstetrical conditions, and in conclusion would say that although the advent of the sex hormones into everyday therapy has been hailed with acclamation and enthusiasm, they must not be regarded as the panacea for all the ills and peculiarities to which the female species is subject.

The chemist has provided us with potent preparations, and it behoves us as clinicians to realise that the indications for their use must be defined and limited, and that their misuse may be fraught with serious consequences. Intelligently and wisely used, they can be of inestimable value.

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CONCERNING CANCER

By F. E. REYNOLDS, M.D., F.R.C.P.Ed.

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Introduction

FOR some years it has been taken as axiomatic that advance in knowledge of medical conditions and processes can be made only by studying them or allied conditions in the lower animals. Undoubtedly much can be learnt by a consideration of comparative pathology, but none the less I would submit in no equivocal terms that much can still be learnt concerning disease by studying it in the human subject. While general morbid processes may be similar in all mammals, most of you will join me in dissenting from the view that you and I are in all respects similar to rats, mice, guinea-pigs and rabbits—the animals largely used in experimental work and on the result of which so much is deduced as to what is applicable to the human being. To-day few will dispute the importance of the psychological factor in any disease, and in this way alone there is a fundamental difference between man and the so-called lower animals.

Most of us men like occasionally to raise our eyes to the stars and to cry with the psalmist of old: "Thou hast made man a *little lower than the angels; Thou hast crowned him with glory* and honour."

A condition rarely met with in human medicine often throws no new light on any aspect of disease; its chief interest is usually its rarity, and as such, if it has expressed itself as a lesion, it has a place, more or less honoured, in a museum. Generally, it is from a consideration of the commonly occurring conditions that knowledge in medicine is advanced, but it so often occurs that owing to their very frequency the recognition of the problems awaiting solution escape our notice.

Malignant growths in general and cancers in particular are among the conditions encountered daily by the physician, by the surgeon and by the pathologist. Again, no subject in human

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control of the proliferation; so long as the reproducing cells are under control the condition is hyperplastic, but when control ceases or has been overcome proliferation is no longer hyperplastic but neoplastic. The phase at which any particular example of cellular reproduction manifests itself in the structural change of local or distant invasion must necessarily be some time after the essential change in the cells in relation to their environment has occurred. As a foundation of this enunciation of the concept of malignancy—one which, after all, is almost a statement of fact—you will recognise the theory known for many years as "Ribbert's Tissue-Tension Theory."

When considering any aspect of malignancy it is of fundamental importance to remember that the process occurs in two phases: firstly, that of initiation, and secondly, that of continuance. The phase of initiation may be long, extending into many years, and to-day some authors believe it is partly owing to this that so many cancers do not manifest themselves until middle life; they believe that it is not so much changes in the cell occurring at that time as the long duration of the initiative phase which accounts for the tumour not having appeared earlier in life. There is some collateral evidence to indicate that in certain instances the stimulus to malignant growth has been active for at least ten years before the neoplasm occurred.

The recognition of the two phases in the malignant process is one which has long been insisted upon by Sir Robert Muir in his teaching and writings; its importance is now generally recognised.

You may have wondered why I confined the title of my lecture to cancer, why I did not use the wider term of malignant growths and so include the sarcomata. Although I do not hesitate to allude to malignant growths of mesoblastic nature where they conveniently illustrate some point to which I desire to invite attention to-day, I have deliberately used the word "cancer," since, except in few instances, I have little conception of the real nature of a sarcoma. Some years ago there occurred in the wards of the Royal Infirmary a rhabdomyoma of the nasopharynx of a girl of eight years of age; when first examined the growth was obviously composed of elements having striped muscle fibres as their normal prototype The patient lived for some six months, and on several occasions during that time portions of the growth were removed for palliative reasons; the degree of structural differentiation of the cells gradually diminished

medicine has caused greater hopes to be raised by many individual workers; on no subject have claims and theories caused the rise and fall of more attention and optimism. A review of those advanced even in the past couple of decades makes one realise how frequently must be invoked the age-old comment, *Sic transit gloria mundi.*

Some General Considerations

With these thoughts in mind I need offer no apology in inviting you to consider for a short time the present-day position of certain questions regarding malignant growths. Naturally, to deal adequately with any one of the subjects which I purpose bringing before you would require far more time than is available, and if on certain issues I draw conclusions which seem to be based on insufficient evidence, I would ask you to remember that each aspect of the subject can be presented this afternoon only in its barest outline.

Little short of a century ago Virchow wrote that no one even under torture could define a neoplasm; since then many definitions have been put forward and every undergraduate appearing for his professional examination in pathology can repeat one or more with satisfactory glibness and complacency. All these assertions define a neoplasm in terms of properties none of which are possessed by every neoplasm. I do not desire to be sophistical, but in passing I ask you to consider whether to-day we can define a neoplasm in precise terms any more than could Virchow when he enunciated his well-known aphorism.

The conception of the quality or property of malignancy is easier to state, and yet it is not so generally realised as it merits. The morbid histologist reporting on the question of malignancy to his clinical colleague bases his diagnosis on the relationship of the neoplastic cell to the surrounding tissue, that is to say on whether the neoplastic cells have invaded the adjacent tissues or have metastasised into distant parts, this must be his criterion since the malignant cell has no constant and specific cytological feature to contrast it with its non-malignant prototype But invasion, and still less metastasis, is not the first or indeed the essential change in the cell which determines its malignant character. At times it is difficult from the structural picture to determine whether the proliferation of tissues is hyperplastic or neoplastic. The essential difference has to do with the general

These chemicals are hydrocarbons, and the substances in the crude product which are carcinogenic belong to three main groups: (*a*) those related to dibenzanthracine, (*b*) those not related to dibenzanthracine but containing the phenanthrene ring system, (*c*) those not containing the phenanthrene ring; only two carcinogenic substances belong to this last group.

As a matter of fact, the first investigation of a chemical substance for its carcinogenic properties was made by B. Fischer, who published his work in 1906. He used Scharlach R. and found that it produced cellular proliferation, but it did not progress to the extent of malignancy. It is interesting to recall that for some time after the publication of this work, Scharlach R. was used in certain surgical cliniques as an ointment to stimulate wounds which were slow in healing.

The study of tar as an etiological factor in the occurrence of cancer—a study made intensively for some years—has not yielded much new information. From this work, however, it has been claimed that if subjected to the stimulus, young patients are just as liable to develop the condition as are older subjects. If this be correct, it is one of the facts against the thesis that ageing tissues are more prone to malignant change.

It is well known that the emanations of radium may be a factor in producing malignant growth. One of the best examples of this is the experience in a New Jersey watch factory, published by Harrison S. Martland and his associates in a series of papers between 1925 and 1931. Briefly the occurrence was as follows: During the years 1917 to 1924, 800 girls were employed painting luminous dials for watches, no more than 250 girls working at one time. The paint consisted of crystalline phosphorescent zinc sulphide rendered luminous by the addition of small amounts of radio-active substances in the form of insoluble sulphates. The general habit among these workers was to point the brush with the lips, and in so doing they swallowed small amounts of the radio-active substance The girls affected had swallowed the paint for periods varying from one to four years or more. A small amount of the paint thus swallowed was absorbed and stored in the reticulo-endothelial system, and especially in the bones of the entire skeleton

Among these workers 18 died of so-called radium poisoning, and in 1931 some 30 others were alive but suffering from typical symptoms. Death occurring among early cases was due to necrosis of the jaw and anæmia, the latter being leucopœnic of

until, shortly before the fatal termination, the neoplasm was composed of spindle cells, that is to say, of cells which from the structural standpoint had differentiated only to the slightest degree. This was a tumour the life history of which could be understood fairly completely; if, however, tissue had been obtained only at the stage when the neoplastic elements showed practically no structural differentiation, I submit it would have been unjustifiable to put forward any speculation as to the nature of the growth. Further, as you are all aware, the cells of most sarcomata are round or spindle-shaped at the time they first come to the notice of the Clinician or of the Pathologist, and I maintain that in many of these cases no idea whatsoever can be formed as to the nature of the tissue which the neoplasm is representing. Merely to label such conditions "sarcomata" is masking our ignorance, possibly deceiving others and, what is far the most dangerous, deceiving ourselves.

Moreover, I scarcely need remind you that certain neoplastic growths which even a few years ago were considered beyond question as mesoblastic are now universally accepted as epiblastic; I refer especially to those neoplasms which until little more than twenty years ago were accepted as lymphosarcoma of the mediastinum and are now known to have their origin in relation to the lining of the bronchial tree; and to "melanomata," many of which are certainly epiblastic in origin.

For the past few years, work on cancer has been mainly concerned with studying three aspects of the disease: firstly, the part played by chemical and physical agents in initiating cancerous growths, secondly, the existence of an infective factor, namely a virus, in their genesis, and thirdly, inherited predisposition to develop malignant growth Let us briefly consider each of these subjects so far as present-day knowledge is concerned.

Chemical and Physical Carcinogenesis

For many years a relationship of the occurrence of cancer to certain industries has been recognised; for example, cancer of the scrotum in chimney-sweeps, associated with soot, epithelioma in shale oil workers, associated with paraffin; mule spinners' cancer, associated with lubricating oils; carcinoma among certain employees in gas works, associated with coal tar, malignant papilloma of the urinary bladder in aniline dye workers.

Malignant tumours of fowls have been particularly studied by P. R. Peacock, but the first of them, due in whole or in part to a filterable virus, was described by Rous in 1911. It had occurred in a Plymouth Rock hen and had been diagnosed as a sarcoma. This was the tumour which is now commonly known as " Rous' sarcoma of the fowl." Many refused to accept Rous' contention that here was a neoplasm produced by an agent separated from its cells, and some refused even to accept the growth as a neoplasm.

To-day not only is the etiological factor of Rous' tumour accepted as being a virus, but eleven out of twenty-seven spontaneous fowl tumours, and these include an osteo-chondrosarcoma, have been proved to be brought into being by a cell-free extract or, to put it shortly, by a virus.

In 1925 an article by W. E. Gye and J. E. Barnard caused much excitement. These authors had been working with Rous' sarcoma and in their paper propounded the thesis that the occurrence of a neoplasm was due to two agents, one a filterable virus common to all neoplastic growths, and the other, " the specific factor," inanimate and peculiar to each tumour. This theory was attractive in that it unified a large number of apparently unrelated facts. Doubts soon began to be cast on the data on which Gye and Barnard's thesis was founded, and the theory has now been generally discarded.

Although it be accepted that a number of neoplasms of spontaneous occurrence in birds are due to viruses, it must not be argued that a similar state of affairs will be found in man or even in mammals. It must be remembered that phylogenic development proceeding from the reptilian stage divided into two great branches—one represented by the present-day bird and the other by the present-day mammal. This development along two widely divergent lines is manifest in many dissimilar anatomical and physiological features characterising birds and mammals.

It is necessary, therefore, to enquire if any neoplastic growths occur in mammals and which are attributable to the presence of a virus.

In 1928 Rhoda Erdmann claimed that a sarcoma occurring in a rat was due to a filterable agent, but several workers have failed to confirm this. In 1936 L. Dorothy Parsons made a similar claim in regard to a sarcoma in a mouse, but again this has not been confirmed.

the regenerative type and not of the aplastic type, as has been erroneously quoted. Later cases showed osteitis so marked as to be crippling.

Martland maintains that the harmful effects were due to the intense destructive effect of alpha bombardment; this gave rise to chronic osteitis with, in some instances, later development of sarcoma.

Lastly, it has been suggested that the high incident of pulmonary carcinoma in the cobalt miners of the Schneeberg district of Saxony—an occurrence noticed since the early part of the sixteenth century—and that among the workers in the pitchblende mines of Joachimsthal in Böhmen may be due to the inhalation of radio-active substances.

Œstrin as a Carcinogenic Agent

Work on the relationship of œstrin to carcinoma was started in 1916 by Lathrop and Loeb, and its more recent exponent has been Lacassagne. Since the work has attracted much attention it is necessary to refer to it, and this is a convenient place so to do.

The workers mentioned, and others, have shown that œstrogenic hormones can be a factor in producing mammary carcinoma, but for this result the ovarian secretion must be present in large amounts and the patient must be one having an hereditary predisposition to develop cancer.

The Infective Hypothesis

For many years some workers have believed that cancer was due to micro-organisms, and in certain cases specific bacteria have been claimed to be the chief factor in the occurrence of malignant growths. These views have met with little favour by the majority, and none of them has survived critical examination and the passage of time

It may be taken, however, that certain non-malignant tumours in mammals, for example the common wart, and certain malignant tumours of birds can be initiated by agents which are generally held to be viruses.

Naturally the question arises here whether a virus is a living micro-organism or something of the nature of an enzyme A mere summary of the matter and of the views advanced would entail a lecture to itself, and I shall not attempt to deal with it here.

computed that twelve days of a mouse's life is the equivalent of one year of the life of a human being.

C. J. Lynch asserts that in mice susceptibility to cancer behaves as a Mendelian dominant and resistance to the disease as a recessive character. M. Slye, however, asserts the opposite.

The question of hereditary predisposition is one which entails ascertaining family histories on a large scale Earlier workers in this direction did not extend their researches widely enough, and the first reliable knowledge was obtained by G. H. M. Waaler. Under his direction some 6000 cases of cancer occurring in Norway during the previous twenty years were studied. Investigators went to particular districts and collected data both from members of the family and from their doctors. At the same time control material was examined

A little later a similar survey of 2472 cases under the direction of W F. Wassink was made in Holland.

The data collected by these two investigations correspond in essential facts, and among the chief phenomena which emerged were :—

Firstly, relatives of cancer patients show a higher incidence to the disease than does the general population. Secondly, predisposition is to some extent determined by sex ; a higher incidence of cancer occurs among the female relatives of a female patient developing cancer than among her male relatives, and *vice versa*. Thirdly, the hereditary predisposition may be related to particular organs ; for example, the relatives of women developing cancer of the breast or of the uterus show a greater liability to have cancer of these organs respectively than does the general population Fourthly, cancer in the male is more often determined by extraneous factors, while in the female hereditary influences are greater.

These deductions have been emphasised in recent years in various papers ; in an address to the Assurance Medical Society in 1937, W. Cramer clearly stated that the statistical data are sufficient to demonstrate the existence of an hereditary factor in man.

Conclusion

My lecture this afternoon has been discursive and has touched upon a number of aspects of malignant growths. This has necessarily been so, since I have endeavoured to indicate the lines along which thought and work on the subject is being directed.

Certain conditions occurring naturally among rabbits are undoubtedly related to a virus. A rapidly fatal disease known as infectious myxomatosis and characterised by masses of gelatinous material, is indigenous to rabbits in South America. There is, however, considerable doubt as to whether the lesions of infectious myxomatosis are neoplastic or inflammatory in nature.

In 1932 R. E. Shope described a subcutaneous fibroma in the cottontail rabbit in the Middle West of America, and showed it to be related to a virus. In 1933 the same author described a cutaneous papilloma of cottontail rabbits, and this is undoubtedly due to a virus Furthermore, a malignant transformation has been observed in domestic rabbits suffering from the disease, although the virus has not been shown to be present in the carcinoma.

To summarise the position of viruses in relation to malignant growths: A virus initiates a number of malignant tumours of fowls and a certain number of non-malignant tumours of mammals; the latter include the cutaneous papilloma of man. In mammals, however, an infective agent has so far not been proved to have a direct etiological relationship to a malignant tumour.

The Hereditary Factor in the Occurrence of Carcinoma

Some years ago it was customary to state that so-called cancer villages, streets, houses and families could be accounted for by the law of chance. It was said, and in fact well said, that the occurrence of cancer in members of a family put forward as examples of a hereditary factor were so many " collections of anecdotes "

It is common knowledge that female mice not infrequently develop a spontaneous adeno-carcinoma of the breast. It is equally well known that to-day families of mice exist in which the majority of the female members develop adeno-carcinoma mammæ, and on the other hand there are families of mice in which the occurrence of this condition is rare. The certainty of susceptibility to carcinoma of the breast of some families of mice and the relative immunity of other families naturally again raised the question of a similar occurrence in man.

It will be understood that the investigation of the matter in mice and in man are in widely different categories The reproduction of mice can be controlled; furthermore, it has been

computed that twelve days of a mouse's life is the equivalent of one year of the life of a human being.

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Further, a consideration of this commonly occurring disease illustrates very forcibly how slowly real knowledge of morbid processes is advanced. It is given to few to make revolutionary discoveries; for the most part progress is a slow and patient discovery of facts each of little significance, but the whole finally building a great edifice of knowledge

MAMMARY CANCER AND THE MENOPAUSE

By E. K. DAWSON

(From the Laboratory of the Royal College of Physicians, Edinburgh)

MAMMARY cancer at an early stage is a localised and curable disease. A Ministry of Health report [1] of an investigation in the Leeds hospitals, analysing end-results in about 350 cases treated by radical operation, showed, in those with microscopical evidence of no invasion of the axillary tissues, a ten-year survival rate of 90 per cent. The chance of survival in these patients was thus approaching nearly that of the entire population of a corresponding age period. But mammary cancer is not often encountered at this early stage. MacCarty of the Mayo Clinic stated [2] that a really early cancer is, in almost all cases, found accidentally. The breast is removed, not because the lesion is malignant, but because the surgeon fears it may be, and histological examination then reveals an early carcinoma. After this early stage, prognosis deteriorates rapidly, for not only do the malignant cells infiltrate the tissues of the mammary area where they are accessible to therapeutic attack, but they enter the lymph stream and later the blood-stream and are thus transported to distant and usually untreatable sites.

Some years ago I made a detailed histological examination of the operative material from a series of 460 mammary cancers at all stages of growth.[3] This investigation showed 85 per cent. invasion of lymph vessels in the mammary area, 70 per cent. invasion of the axillary tissues, and 31 per cent. invasion of blood vessels in breast or axilla or both areas, a commentary on the late stage of tumour growth at which these patients came for treatment. Lynham [4] estimated that 75 to 95 per cent. of all malignant mammary cases show spread beyond the actual breast when first examined.

This position is, of course, well known, but it needs constant emphasis to prevent delay in the diagnosis of any mammary lesion. An "obvious" mammary cancer, that is, one which shows the typical text-book picture clinically, is probably in the majority of cases already beyond cure, though not beyond

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palliation and some prolongation of life. It should be remembered that the average duration of life in untreated mammary cases is a little over three years after the discovery of the tumour.[5]

In all doubtful cases, delay in treatment is only justified if there be proof that the condition is not malignant, and at our present stage of tumour knowledge the only proof is histological. The delay in treatment due to the patient's ignorance, or lack of observation or possibly deliberate self-deception, is, at present, largely outside medical control. The patient delays because she fears cancer and assumes it is hopeless ; cancer becomes hopeless because she delays. This is a vicious circle which can only be broken into by the production, publication and acceptance of much improved survival figures with standardised controls. The establishment of a wider medical service providing facilities for periodic examination with a preventive outlook and without emphasis on tumour growth would bring more cases of cancer under observation at an early and curable stage, in the same way that mass radiography is expected to reveal early lung trouble.

Delay in diagnosis by the clinician would be largely prevented if the broad principle were accepted that very few considerations apart from a young age rule out the possibility of mammary cancer. As the age period rises, the probability of cancer increases. This is illustrated by a recent survey by Colonel Harvey and myself of all mammary cases reported on, in one year, at this laboratory.[6] In the period under review, 274 cases were reported, a comparatively small number but sufficient for analysis. The female cases comprised 97 per cent. ; the male cases are excluded from the following figures :—

Age.	*Nature of Lesion*
Over 65 years	All cases carcinoma
,, 60 ,,	95 per cent carcinoma
,, 55 ,,	92 ,, ,,
,, 50 ,,	85 ,, ,,
But *under* 40 ,,	85 ,, were benign
,, 30 ,,	All were benign

There was thus a complete reversal of the benign-malignant ratio between forty and fifty years In other words, our figures showed that under forty years, in material sent to the laboratory for examination, the likelihood of cancer was only 1 in 7, but over fifty years it became 6 in 7, with the likelihood of a benign condition now only 1 in 7. In the curve of malignancy during the

"reversal period"—forty to fifty years—occurs the point at which benign and malignant tumour percentages were equal. No sarcoma was found among the malignant cases; more than half of the non-tumour lesions were single or multiple cysts.

These figures, and indeed all mammary cancer figures, bring out the same point, that in diagnosis the age of the patient is a factor which carries much weight. Sarcoma may be found at almost any age but tends to occur at the earlier age periods; carcinoma, a much more frequent form of malignant growth, is predominantly a disease of middle and later life. Hence the expression "the cancer age," usually ascribed to the forty to sixty year period. The acceptance of the idea of middle and later life as a "cancer age" implies some relation between the ageing process as such and tumour growth, or the prolonged duration of some carcinogenic stimulus, the effects of which emerge at this later period of life. These two possibilities are not mutually exclusive alternatives, as the ageing process in the body may itself be associated with the production of a carcinogenic factor, metabolic or other. Among the many lines of investigation of cancer genesis, little attention has been given to the ageing process as such in tissues and organs, though Goodpasture discussed tumour growth, especially testicular, in relation to senescence in dogs.[7] As far as the breast is concerned, I have been unable to find any adequate description of the normal involutionary and atrophic changes which occur with age. Yet it is in the mamma and the genital system of which it forms a part that both recurring and permanent involutionary changes are most evident during life, and these are the organs which provide by far the largest cancer incidence in the female subject

The normal growth and functioning of mammary tissue is primarily dependent on the ovarian hormones; the rhythm or periodicity of their action is apparently governed by the anterior lobe of the pituitary gland through its gonadotropic and lactogenic hormones. A more specific consideration of the action of these hormones is beyond the scope of my general treatment of the subject here. It is possible that adult tissue normality depends, to a large extent, on the balanced working of all the endocrine glands functioning as a correlated system, but we may say that it is the ovarian stimuli which promote and control mammary growth and hold these tissues, directly or indirectly, at a functional or potentially functional level. The subsidence of reproductive activity with the gradual loss of ovarian stimuli during the

palliation and some prolongation of life. It should be remembered that the average duration of life in untreated mammary cases is a little over three years after the discovery of the tumour.[5]

In all doubtful cases, delay in treatment is only justified if there be proof that the condition is not malignant, and at our present stage of tumour knowledge the only proof is histological. The delay in treatment due to the patient's ignorance, or lack of observation or possibly deliberate self-deception, is, at present, largely outside medical control. The patient delays because she fears cancer and assumes it is hopeless; cancer becomes hopeless because she delays. This is a vicious circle which can only be broken into by the production, publication and acceptance of much improved survival figures with standardised controls. The establishment of a wider medical service providing facilities for periodic examination with a preventive outlook and without emphasis on tumour growth would bring more cases of cancer under observation at an early and curable stage, in the same way that mass radiography is expected to reveal early lung trouble.

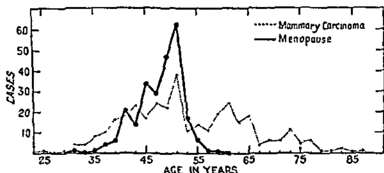
Delay in diagnosis by the clinician would be largely prevented if the broad principle were accepted that very few considerations apart from a young age rule out the possibility of mammary cancer. As the age period rises, the probability of cancer increases. This is illustrated by a recent survey by Colonel Harvey and myself of all mammary cases reported on, in one year, at this laboratory[6] In the period under review, 274 cases were reported, a comparatively small number but sufficient for analysis. The female cases comprised 97 per cent., the male cases are excluded from the following figures.—

Age.	*Nature of Lesion*
Over 65 years	All cases carcinoma
,, 60 ,,	95 per cent carcinoma
,, 55 ,,	92 ,, ,,
,, 50 ,,	85 ,, ,,
But *under* 40 ,,	85 ,, were benign
,, 30 ,,	All were benign

There was thus a complete reversal of the benign-malignant ratio between forty and fifty years In other words, our figures showed that under forty years, in material sent to the laboratory for examination, *the likelihood of cancer was only 1 in 7, but over fifty years it became 6 in 7, with the likelihood of a benign condition now only 1 in 7.* In the curve of malignancy during the

growth, an active, progressive neoplasia, at a time when the mamma should normally be retrogressing to atrophy and aplasia.

Before illustrating the cellular changes which eventuate in carcinoma, I must mention two terms which describe the types of epithelial proliferation found in mammary tissue. These terms, *adenosis* and *epitheliosis*, were introduced and illustrated in an earlier study of "Carcinoma in the Mammary Lobule and its Origin,"[9] and do not in themselves necessarily carry a pathological significance. They are illustrated in diagram form in text Fig. 2 and in Figs. 1 and 2, Plate I. *Adenosis* describes the glandular hyperplasia or overgrowth which produces more and larger lobules of normal or exaggerated physiological pattern; it is found in the breast most characteristically during pregnancy (Fig. 1), but is also evident to a lesser



The age-incidence of mammary carcinoma and the menopause.

Fig 1

degree during adolescence and the climacteric period (Figs. 7-11). Adenosis is apparently synonymous with Cheatle's term mazoplasia, which he describes as "*a physiological rather than* a pathological process" and "almost universally present in some degree until the menopause in normal breasts of all women who have borne children"[10] Cheatle associates with the increased number of small glandular elements formed in mazoplasia, slight distension of the lobular structures by desquamated epithelial cells and possibly some incidental stroma activity but no cyst formation Geschickter[11] extends the conception of adenosis to include small cysts, minute adenomas and papillomas and diffuse fibrosis, thereby giving the term a definitely pathological significance. I think it simplifies descriptions of mammary tissue activity to adhere to the earlier definition of adenosis as a purely glandular overgrowth, and it is used here in that sense.

climacteric implies the lessening of this control and leads, after the menopause, to the involution and atrophy of both genital and mammary tissues. But ovarian subsidence has also a systemic significance, for it involves a readjustment of the whole endocrine system with the possibility, in extreme cases, of what has been called a "pluriglandular crisis" A French cynic has remarked that our therapeutic ignorance of the management of the menopause is largely responsible for the almost universal unpopularity of the mother-in-law. Certainly a considerable proportion of women show at this period some symptoms of instability, often unrecognised and therefore untreated. These symptoms suggest that the effort of endocrine readjustment falls not only on the pituitary gland, which is specially linked with the ovary, but also on the thyroid, the adrenal and possibly the pancreas. The main effort towards readjustment, however, seems to be made by the pituitary gland, with a compensatory secretion of the follicle-stimulating hormone of the anterior lobe. This is suggested by the palliative effect of œstrin therapy at this period, œstrin having normally an inhibiting influence on the production of this pituitary factor. The effect of œstrin is apparently to keep down the pituitary hormone until, with progressive involution, stabilisation is established. This effort at endocrine adjustment points to the likelihood or at least the possibility of genital and mammary tissue disturbance during the climacteric period and later, and the need for further investigation by the clinician, the endocrinologist and the chemist, as well as the pathologist

This view receives some confirmation from an investigation I made of the age incidence of the completed menopause and also of the age at surgical treatment for mammary cancer in two unrelated series of cases of about 300 each.[8] The menopausal figures were obtained at the Bruntsfield Hospital for Women and Children, where menstrual and menopausal data are recorded in all cases as a routine, a procedure I would specially advocate for mammary cases The two graphs are shown in text Fig 1, with the peaks coinciding at the same age, fifty-one years, which here signifies the fifty to fifty-two year period The period preceding the peak, forty to fifty years, seems to be a dangerous age, the "reversal period" already mentioned Fertility is declining, for pregnancy is comparatively infrequent after forty and, at the same time, mammary lesions, as indicated by the figures noted above, show a rising probability of cancer It seems relevant to ask what are the tissue changes which lead to malignant

diminution of the glandular content resulting in smaller lobules and fewer ducts, a reversal, as it were, of the process by which the mature glandular structure was built up. This slow atrophy is associated with fibrosis, often with much hyaline change and there may be considerable increase of both fatty and elastic tissues. This retrogression is, however, often, if not usually associated with proliferative changes, and it is these which need examination in more detail. Ewing [14] considered that though such proliferative activity "does not properly belong to normal involution, it is so frequently observed that its presence in moderate degree must be included in the usual picture of involution, though a pronounced degree of proliferation should be classed with chronic productive mastitis" My examination of apparently normal tissue of the climacteric and post-menopausal periods supports this position, in showing in almost all cases evidence of some degree of present or previous epithelial proliferation. Greater activity may produce diffuse or localised enlargements which lead to operative removal, and a large amount of such tissue from patients at ages ranging from forty-one to fifty-six years has provided material for this study of the various types and degrees of proliferation associated with involution Much of the tissue was cut in whole breast sections and in more than one plane. The proliferative appearances fall into one or other of the two types already described, adenosis and epitheliosis, but a pure picture of either condition is rarely observed, the lesion is usually complex, with varying degrees of both processes evident.

The adenosis may be localised or involve the whole mammary tissue; clinically, the enlargement produced may vary from time to time, but no invariable association with irregular menstruation could be made out in the cases where data were available. A generalised adenosis is shown in Fig. 7, in a breast removed from a patient of forty-nine with hæmorrhagic discharge from the nipple due to a small benign papilloma (not seen in this plane of sectioning). The *corpus mammæ* was described clinically as "more or less normal in size and texture"; microscopically it showed a typical adenosis of regular pattern (Fig 8). A localised adenosis may present a doubtful clinical picture; Fig. 9 shows the proliferation limited to an area at the periphery and forming an indefinite thickening suggestive of carcinoma in a woman of fifty-two years. Microscopical examination after radical amputation showed only adenosis of a very regular

It may, of course, be qualified by various descriptive additions if a varied pathological picture be present. The second term, *epitheliosis*, describes the multiplication of epithelial cells within existing ducts and ductules without the formation of new glandular elements (Fig. 2). This proliferation, when examined, may be of solid or papillary character or may form a multi-layered cell lining. These various types are illustrated in the plates. In the early stage of mammary duct and lobule formation from the embryo onwards, the glandular structures consist of solid cords of epithelial cells which later are canalised. Small solid gland

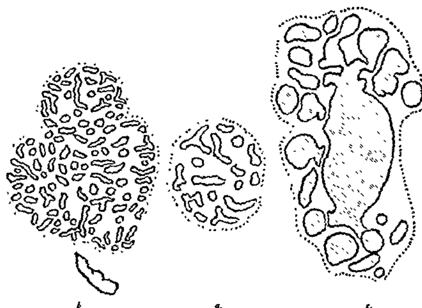


Fig. 2.

a. Average size normal adult lobule *b*. Enlarged lobule—*adenosis*.
c. Epithelial cell proliferation filling the lobular structures—*epitheliosis*

elements at any age may thus carry little significance. Epitheliosis, however, implies a greater degree of cell multiplication with some gland distension, and though this proliferation is frequently followed by degeneration and desquamation, epitheliosis, in contrast to adenosis, is often a potentially abnormal cell activity.

The developmental and functional phases of normal mammary tissue were studied in detail in two earlier papers [12, 13] as a basis for assessing pathological growth Some of these phases are seen in Plate I, which also illustrates a normal menopausal (Fig. 5) and a senile quiescent picture (Fig. 6). In general, menopausal retrogression or involution is shown by a slow

and cysts, which produce the doubtful or suspected lesions of this period. Epitheliosis occurs primarily in ducts, large and small, but it may extend to involve the small lobular structures. Later, the proliferated cells tend to degenerate, with the formation of cysts. These cysts are of two distinct types. One type, the characteristic cyst of "fibrocystic disease" or "chronic cystic mastitis," is often called the eosinophile or pale cyst because of the very distinctive large, pink epithelial lining cell, difficult to show without colour (Figs. 21-23). It is often described as of sweat-gland type or even actual sweat-gland tissue, but it has no demonstrable connection in the breast with sweat glands. An early stage of epitheliosis of this pale cell type often shows papillary tufts in the dilating ducts (Fig. 22); later, as the cysts enlarge, they tend to coalesce by the pressure atrophy and breakdown of adjacent walls, thus forming the large "blue-dome" cysts typical of the advanced condition. A typical cystic breast, with larger and smaller cysts lined by little or no epithelium, is shown in Fig. 24. This was a bilateral case, treated by double simple amputation, in a patient of forty-seven years (Figs 25, 26); the plane through the nipple shows one large cyst among numerous smaller ones, in both breasts. The nature of this eosinophile or pale change is not known; tests for mucin, glycogen and fat have all proved negative,[17] but it is in my opinion a degenerative change and the end stage is atrophy and complete quiescence. I have found no evidence that it gives rise to carcinoma, the so-called sweat-gland carcinoma of the breast.[18]

If this were the only type of mammary cyst, we could say with considerable assurance that cystic disease of the breast is not a dangerous condition, but most sections of cystic tissue show, in addition to the pale epithelial cyst, another type where the degenerative change is of a fatty nature, with the production of colostrum-like cells. The progressive stages of its formation are shown in Figs. 27-32. The early stage shows little distension of the duct, though the lumen is largely filled with the fatty, desquamated cells of epithelial origin (Fig. 27); a further stage shows a mixture of intact and fatty cells forming the wall of the cystic duct, as well as fatty cells in the cavity (Fig. 28). Later still, the proliferated epithelial cells degenerate into masses of these colostrum-like cells, which may rupture the basement membrane and escape into the surrounding stroma, which reacts with fibrosis and some degree of lymphocytic cell infiltration (Fig. 29). This reaction outside the remnants of the basement

pattern (Fig. 10) almost identical with that seen in early pregnancy. In some cases the lobules, though of physiological pattern, may show considerable variation in size (Fig. 11); in others, associated with hypertrophied lobules, there are areas of active fibrosis separating the ducts and small gland elements and suggestive of a very early stage of fibroadenomatous growth (Fig. 12). Minute defined fibroadenomas, single or multiple, are also frequently found in the hyperplastic involuting breast.

In the examples illustrated, the lobules, though much increased in size and number, are of normal or exaggerated physiological pattern—the picture which used to be called "chronic lobular mastitis." This climacteric adenosis is followed by a fibrosis in which the glandular structures show collapse, atrophy and gradual obliteration (Figs. 13, 14). High-power examination of such a field shows numerous fibroblasts round collapsed small ducts and terminal elements which can, however, still be identified by their basement membrane (Figs. 15, 17). The recognition of this fibrosing picture is important. It is the appearance which Bloodgood of Johns Hopkins University[15] described and illustrated as one of the "border-line tumours." He followed many of these cases for over twenty years, however, and none of them, after even limited resection, showed axillary involvement or died of carcinoma. Ewing's experience agreed with Bloodgood's; he called the condition fibrosing adenomatosis and found it was frequently mistaken microscopically for carcinoma.[16] An actual scirrhous carcinoma (Fig. 18) is shown for comparison, with a small unaffected duct in the middle of the infiltrated area The axilla was invaded in this case. Adenosis followed by fibrosis and quiescence is apparently the usual form of lobular involution with the menopause, but other types are found where a periductal fibrosis (Fig 19) or the formation of a thickened hyaline basement membrane (Fig 20) gradually obliterates the small lobular structures. I have found no evidence that adenosis as such becomes malignant—that is to say, that adenosis becomes adenocarcinoma. It *is essentially* a physiological proliferation, only pathological at the climacteric and menopause because of its time incidence, its exaggeration and its usually irregular distribution. Clinically, it is described as giving a resistant, saucer-like edge to the *corpus mammæ*, if fairly generalised; but if localised, it may form an indurated area of doubtful import.

Climacteric proliferation of a purely adenosis type may be infrequent. It is usually found in association with epitheliosis

A short note on two instructive cases will illustrate some of the points raised by these descriptions. The first, a patient of forty-seven years, gave a characteristic climacteric history of intermittent swelling of both breasts with some pain as well as irregular menstruation. The enlargement was more obvious in one breast and this was removed by simple amputation, as it suggested a generalised cystic condition The whole breast in the nipple plane is seen in Fig. 42. Routine small sections made at the time confirmed the clinical diagnosis, showing pale cysts with practically no lining cells and some patchy adenosis. A slice of the whole breast was embedded for later large section preparation, but not actually cut for over three years and not examined for seven years. The large section revealed a small but definite carcinoma near the largest cyst (at x), with early infiltration of the adjacent fat. The microscopic picture is shown in Fig. 43. This patient is alive and well twenty-two years after the simple amputation; neither the surgeon nor the patient knows that the condition was malignant.

The second case is the reverse side of the picture. Ten years ago part of a breast was removed from a patient of forty-one years for localised cystic disease. Recently the remaining tissue was amputated for a tumour suggestive of carcinoma; microscopically, it showed an infiltrating growth of very glandular type with much fibroblastic (scirrhous) reaction and invasion of the surrounding fat. The area seen in Fig. 44 shows malignant epitheliosis before invasion, as well as the infiltrated tissue and two atrophic pale cysts. In other parts the picture was predominantly a quiescent cystic condition.

These descriptions and illustrations justify the uncertainty with which the climacteric and menopausal breast with cysts is regarded. There has been and still is much discussion of the question: What is the relation of cystic disease or "chronic mastitis" to carcinoma? But chronic mastitis, if conveying an identifiable clinical picture, is not a defined pathological entity, but a complex lesion with varied types and degrees of epithelial activity and degeneration Two of these, adenosis and the pale cyst, give, in my experience, no evidence of transition to carcinoma. The fatty cyst may also become completely degenerate and quiescent, but its partial degeneration leaves cells which may eventually show malignant change. There is, in addition, an epitheliosis which seems to pass into a malignant phase with little or no obvious earlier degeneration when examined. These

membrane is also seen at higher magnification in Fig. 30. In some cases, when examined, the wall of the cyst is lined by masses of cholesterol crystals and foreign-body giant cells (Fig. 31). The final stage is usually a collapsed and convoluted cyst, with a thick fibrous wall and little or no epithelial lining (Fig. 32). The cyst at this stage is often fixed in the mammary tissue and the fibrosis may draw in the nipple and present a deceptive clinical picture, but trans-section of the area shows only the collapsed, atrophic cyst.

All the proliferated epithelial cells in a fatty cyst may, however, not degenerate, and if they persist, there is the possibility of progressive activity, with the emergence of a malignant cell type. Fatty cysts rarely attain a great size; the characteristic *cyst of cystic disease of the breast is the "blue-dome cyst,"* which, as already described, is the end-stage of the eosinophile or pale cell type. In the involuting breast both types are frequently found, associated often with diffuse adenosis. The so-called chronic mastitis picture is thus extraordinarily complex and varied. It may show predominantly an irregular, non-lobular adenosis, with small cysts and only slight epitheliosis (Fig. 33); or an irregular picture of small cysts with both fatty and pale change (Fig. 34). Combined with these cysts, there may be present ducts filling up with epithelial cells which show little degeneration, but are still more or less of normal mammary gland character (Fig. 35). Larger cysts may contain papillomatous growth, complex in structure but benign and with no evidence of invasion (Fig. 36). Even when the predominant and obvious feature is the blue-dome cyst, there may be also evidence of an active epitheliosis as in one of the breasts of the bilateral cystic case already mentioned, which showed near the large atrophic cyst, a small complex and active papilloma (Fig 26, x). The outcome of an epitheliosis which shows little or no degeneration is uncertain, especially when it is possible that areas outside the planes examined may show more advanced activity. The early stages of this epitheliosis are obviously benign (Fig. 37); the cell type in Fig. 38 is more doubtful The breast from which the section shown in Fig. 39 was prepared was definitely malignant in other areas, with tumour in the axilla, though this field shows no invasion of the stroma A malignant duct at higher magnification from the same tissue is seen in Fig 40, also at the pre-invasive stage. Both benign and malignant intraductal cell proliferation is shown in Fig. 41, as well as an infiltrated area.

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various histological possibilities underlie the essential problem of the doubtful or suspected mammary condition, a problem for the surgeon no less than for the pathologist.

These degenerative and proliferative appearances are illustrated here from mammary tissues of the climacteric and early menopausal periods. They appear to be associated with the instability produced by hormonal readjustment during these phases of mammary involution, but much further investigation is required regarding the specific stimuli involved in the human subject. The adenosis points to some influence, probably of pituitary origin, compensatory to ovarian decline. The fatty cyst with its colostrum-like cells suggests a perverted lactation product, lactation not of the terminal gland elements as in normal lactation, but of the ducts or ductules, which in the human subject do not show functional activity. Such activity may be due to the lactogenic factor also from the pituitary, and biological assay of the cyst contents might throw light on its nature and origin. Behan [19] states that " colostrum contains a large quantity of œstrone, and this has likewise been demonstrated in cystic cancerous breasts." The pale cyst remains a problem both in its chemical and hormonal aspects. There seems little doubt, however, of its essentially atrophic character. The remaining type of activity, the progressive conversion of the hyperplastic, proliferating epithelium into definitely malignant cells, brings us up against the essential problem of carcinogenesis and the factors which lie behind the malignant change. The process in the breast supports findings in other fields, for example, in experimental carcinogenesis and the occupational cancers, that malignancy is not a sudden development but the end-stage of a long-continued process. In the mamma, the unstable, doubtful or proliferative period coincides in general with ovarian subsidence; in the majority of cases the unstable tissue passes over into quiescence and slow atrophy, but in a minority the proliferation is progressive with the later emergence of definite carcinoma. This transition to malignancy may be due to one or to a number of causes. It may be due to—

(*a*) the loss of ovarian control over normal growth and stability of tissue in the mamma—that is, nothing new may be added to the cells but something normally present is removed and proliferation not directed to function emerges and continues ; or

(*b*) the action of other stimulating growth factors which are given opportunity as ovarian control subsides; or

(*c*) some expressly carcinogenic principle, formed possibly by perversion of sterol metabolism, because hormonal control is absent or aberrant; the instability of the mammary tissues at the time would then act as a predisposing factor.

The large proportion of mammary and genital cancers, in relation to the total malignant tumour incidence in the female subject, lend some probability to all three conceptions.

These ideas are vague, tentative and speculative but they suggest the need for more co-operation among all who are working in the attack on cancer. Such co-operation could consider the cancer patient as a whole and not merely as the victim of a localised disorder, to be treated by one or other specialist. In this question of co-operation a word to the medical students who may soon be responsible for sending tissues from hospital to the pathologist may not come amiss. Professor Ewing, whose recent death reminds pathologists of the debt they owe him, deprecated the request for a pathological diagnosis in the absence of the clinical, operative and radiological data necessary for a full understanding of the lesion. We of a lesser breed make smaller demands, but in the diagnosis of mammary and genital conditions, the pathologist needs the essential facts, such as age, married status, parity and duration of the trouble, as well as the signs and symptoms, if his report is to be really helpful to the clinician.

The ground I have briefly covered is well-surveyed country and presents few new features, but it still holds dangers even for the experienced traveller and one or two signposts may not be superfluous.

For the pathologist the problem is, as always, accurate diagnosis. The adenosis picture, even when complex, irregular and fibrosing, presents little difficulty when once recognised, though, as Ewing notes, "fibrosing adenomatosis" gives rise to a mistaken diagnosis of cancer more often than any other condition.[16] In his experience such cases did not recur even after limited resection. The picture often needs high-power examination, especially when a small piece of tissue provides few landmarks. Its essentially benign and later atrophic character may be accepted. It is, however, usually associated with epitheliosis and cyst formation and thus brought into the category

of the doubtful or suspected lesions. The eosinophile or pale cyst, which is the main feature of fibro-cystic disease, is evidence of a degenerative process and, in my experience, has no genetic relation to malignant growth, but again it may be only one feature of a complex and varied picture. The outcome of the fatty cyst is doubtful. It may show an end stage of complete quiescence with fibrosis and contortion of its thickened wall, but on the other hand, after a phase of epithelial proliferation and fatty degeneration, some cells may survive and undergo a cancerous change. The intermediate picture of extensive but apparently non-malignant cell proliferation presents the really difficult histological problem in pathological diagnosis, especially when the necessarily restricted number of fields examined microscopically withholds evidence of possibly more advanced changes in other areas.

For the surgeon, the doubtful mammary lesion of the forty to fifty year period especially also presents difficulties. If earlier diagnosis of mammary cancer is secured, the border-line cases will increase in number and the pathologist is not ashamed to confess that he can give no positive verdict if only a small piece of tissue be submitted. If this shows no cancer, he can still give no assurance regarding the condition of the rest of the breast. It is difficult for the pathologist not to be biased in favour of simple amputation in these doubtful mammary cases of middle age, when limited resection of a suspected area has not infrequently revealed a histological picture of definite malignancy. This diagnostic mastectomy was discussed and advocated in an earlier study of doubtful mammary tumours.[20]

The mammary lesions which become evident in the climacteric and post-menopausal periods would seem to be a field for investigation of the endocrinologist, the chemist, the gynecologist and the radiologist equally with the surgeon and the pathologist, especially if we consider the mamma as part of the genital system. As far as I can gather, the clinical correlation of mammary and genital disturbance with biological assay is largely an unexplored field. The gynecologist may be dangerous when he wanders outside the pelvis, as the general surgeon may be when he ventures within it—an inevitable penalty for specialisation—but mastopathias and metropathias might throw mutual light on each other, in incidence and in therapy if not in causation, and a fruitful field of study may lie here. There is also a possible relation between the cystic breast and the cystic ovary. The

hormonal instability during the readjustment period of middle life might give scope to the endocrinologist to elucidate minor as well as major symptoms and thus throw some light on the factors which lead to disordered growth and eventually to cancer.

The investigation of mammary tumours has been, and to a large extent still is, the foundation of cancer pathology, and I can end appropriately with the illuminating dictum of the great German surgeon and pathologist, Billroth, " die Mamma ist die Amma der Geschwulstlehre."

I am indebted to the Superintendent of the Laboratory, Lieut.-Col. W. F. Harvey, for much helpful discussion of points raised in this paper. I also wish to acknowledge the generous assistance of the Carnegie Trust for the Universities of Scotland towards the cost of illustration.

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ILLUSTRATIONS

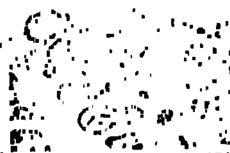
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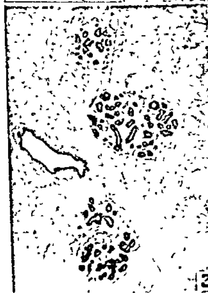
Fig. 4.—Lactating tissue with active secretion

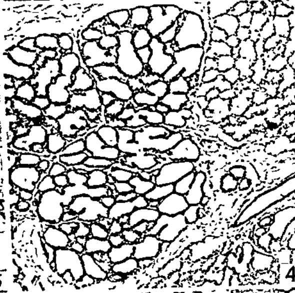
FIG. 5.—Menopausal involution with fibrosing lobules; aged 53.
FIG. 6.—Quiescent atrophic mammary tissue, with ducts, some dilated, in an inactive stroma; aged 73.
FIG. 7.—Generalised adenosis without clinical enlargement; aged 51. Breast removed for discharge from a small papilloma near nipple; not shown in this *plane of sectioning*.
FIG. 8.—Adenosis, same tissue as in Fig. 7, showing enlarged lobules of physiological pattern.
FIG. 9.—Localised adenosis forming an ill-defined indurated area suggestive clinically of carcinoma. Amputation. Aged 52.
FIG. 10.—The suspected area in Fig. 9 showed adenosis only; no tumour was found. *Cf.* Figs. 8 and 9 with Fig. 1; all show hyperplastic lobules of physiological pattern.
FIG. 11.—Adenosis, still lobular in pattern but tending to irregularity in size; aged 51.
FIG. 12.—Enlarged lobule on the right associated with fibrosis round irregularly distributed small duct structures, suggestive of very early fibroadenomatous growth.
FIG. 13.—Enlarged lobule with duct, showing collapse of terminal structures with fibrosis.
FIG. 14.—More advanced fibrosis affecting especially the centre of an enlarged lobule; this "collapse picture" is very similar to that seen in post-lactation involution.
FIG. 15.—High-power view of a small area from Fig. 14; many of these cells are fibroblasts round small collapsed gland elements.
FIG. 16.—Periphery of a greatly enlarged involuting lobule, with more advanced fibrosis.
FIG. 17.—High-power view of an area seen in Fig. 16, with active fibrosis, especially in the lower half. Many other lobules in the section showed this fibrosis at different stages. There was no question of carcinoma. This is Bloodgood's *"border-line" tumour and Ewing's fibrosing adenomatosis*. Their experience emphasised its essentially benign nature.
FIG. 18.—Carcinoma of infiltrating scirrhous type, for contrast with Fig. 17. The axillary lymph nodes were invaded in this case.
FIG. 19.—Another type of lobular involution, with periductal fibrosis obliterating the terminal structures.
FIG. 20.—Another type, showing, in the centre of the large lobule, the broad hyalinised basement membrane with epithelial cell atrophy, also some collapse with fibrosis on the right.
FIG. 21.—Showing, on the right, a group of eosinophile or pale gland structures, enlarging to form small cysts, with early desquamation and degeneration; normal small ducts on the left.
FIG. 22.—Part of a group of the pale glands, with small papillary outgrowths and epithelial debris in lumina.
FIG. 23.—A further stage of cyst formation, parts of several cysts are shown. The pale change is, in my opinion, a post-proliferative degeneration which, by the breakdown of adjacent walls, gradually forms the "*blue-dome cyst*," with little or no epithelial cell lining.
FIG. 24.—Whole breast section of a bilateral case of cystic disease, showing numerous small cysts of pale, atrophic type, aged 47.
FIGS. 25 and 26.—Sections through the nipple plane of both breasts in this bilateral case (*cf.* Fig. 24), showing the large cyst in each, near this in Fig. 26 is a small complex papilloma (*see text*).
FIG. 27.—Early stage of the "fatty cyst," with some dilatation of the duct by many fatty, colostrum-like cells.
FIG. 28.—Fatty cyst, with proliferated epithelium and fatty cells forming a thickened wall, many fatty cells also in lumen. These fatty cells are degenerated epithelium.
FIG. 29.—A further stage of fatty degeneration, down to the basement membrane, which shows rupture in parts with the fatty cells outside the duct wall.
FIG. 30.—Showing part of a fatty cyst with ruptured wall and the fibrous tissue proliferation round the extruded fatty cells.
FIG. 31.—A later stage, with an ill-defined cyst wall, the fibrous tissue shows many clefts representing *cholesterol crystals and foreign-body giant cells*.
FIG. 32.—The end stage of the fatty cyst, with collapsed and convoluted thickened fibrous tissue wall. The fixation of this type of cyst to the surrounding tissues



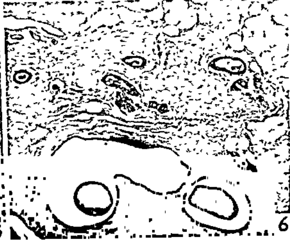




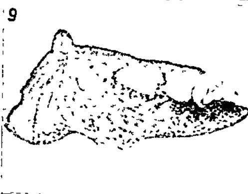
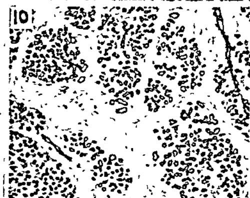









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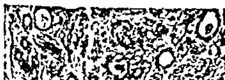
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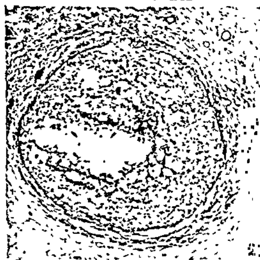
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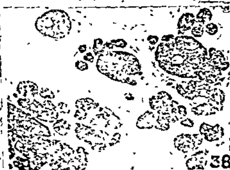

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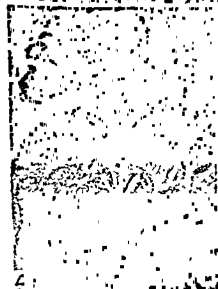

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may produce a very doubtful clinical picture, especially if it lies deep in the *corpus mammæ*.

FIG. 33—Adenosis of diffuse, non-lobular pattern, with small dilated ducts and some epithelial proliferation inside the glands

FIG. 34—Another irregular picture associated with involution, with more epithelial activity and small pale cyst formation.

FIG 35—Epitheliosis filling up small cysts; there is also a small pale cyst, top centre and a fatty cyst filled with colostrum-like cells; the usual varied picture in involution

FIG 36—Epitheliosis of papillary type. These small growths are frequently multiple in one or several ducts and usually show little evidence of degeneration or retrogression.

FIG 37—A small duct filled with proliferated cells of benign type; a little fatty degeneration

FIG. 38—Small ducts and lobular structures with epitheliosis of a doubtful cell nature,

simple amputation. Details in text.

FIG. 43—Part of the malignant area at X in Fig. 42; it had begun to infiltrate the adjacent fat.

FIG. 4

carcinoma

in providing complete and efficient treatment for the population, but also in enabling us to evaluate the advantages or disadvantages of the various methods of treatment at present employed in a manner not hitherto possible. Under existing conditions, and when surgery is the only method of treatment employed, it is probable that not more than 20 per cent. of all cases of cancer of the breast (treated and untreated) coming to a large general hospital survive five years.

In any one centre the problem is somewhat less complex and the difficulties of selection can, to some extent, be overcome. Comparison of results may be made, provided that all cases are divided into groups according to the stage of advancement of the disease at the time treatment is undertaken. Cases in the same stage of advancement may then be compared with reasonable accuracy. The method of staging adopted for this paper is that suggested by Dr Ralston Paterson of Manchester, and is as follows :—

Stage I.—The growth is confined to the breast. Involvement of the skin directly over and in continuity with tumour does not affect staging, provided that the area involved is small in relation to the size of the breast.

Stage II.—As Stage I, but there are palpable mobile glands in the axilla.

Stage III.— The growth is extending beyond the *corpus mammæ* as shown by:

(*a*) The skin is invaded or fixed over an area large in relation to the size of the breast.
(*b*) The tumour is fixed to underlying muscle. Axillary glands may or may not be palpable, but if glands are present they must be mobile.

Stage IV.—The growth has extended beyond the breast area, as shown by:

(*a*) Fixation or matting of axillary glands indicating extension outside the capsule.
(*b*) Complete fixation of tumour to chest wall.
(*c*) Secondaries in supraclavicular glands.
(*d*) Secondaries in skin wide of tumour.
(*e*) Secondaries in opposite breast.
(*f*) Distant secondaries, *e g.* bone, liver, lung, etc.

THE VALUE OF POST-OPERATIVE RADIOTHERAPY IN CARCINOMA OF THE BREAST

By R. McWHIRTER

(Radiologist, Royal Infirmary, Edinburgh)

CARCINOMA of the breast is a comparatively common disease and, in women, accounts for approximately one-fifth of all the deaths from cancer. This figure is all the more remarkable in view of the fact that in the treatment of cancer, the breast is one of the sites in which the best results are obtained. When the incidence of cancer in each anatomical site is considered, it is probable that approximately one quarter of all cases of cancer in women occurs in the breast

The average age in the following series of cases was 55·5 years, so that not only is the incidence high, but the disease appears at a comparatively early age. The youngest patient was twenty-four years old.

Difficulty of Comparison of Results from Different Methods of Treatment.—It is extremely difficult to determine accurately the results obtained from the various methods employed in the treatment of carcinoma of the breast. Many tables of figures have been published, but these merely indicate the survival-rates of the cases accepted as suitable for a particular method of treatment. By careful selection of cases it is a simple matter to produce good results by any method which the author has devised or chooses to advocate. Such figures are of little help when one wishes to determine the value of a particular method of treatment applied to *all cases* of cancer occurring in the breast. Such difficulties will not be overcome until the results, obtained from the application of one method of treatment to all cases occurring in a large population unit, are compared with the results of a different method applied to all cases in another large unit of population, it being clearly understood that no cases—even untreated cases—are excluded from the total on which the percentage success is based. The future regionalisation of medical services may, therefore, play an important part, not only

Read 4th March 1943

Methods of Treatment selected for Comparison.—The primary object of this paper is to demonstrate the effect produced by post-operative radiotherapy. It is necessary, therefore, to select two groups of cases—those treated by operation alone, and those treated by operation and post-operative radiotherapy. A certain standard must be laid down for each group and the standard selected was as follows:—

Operation Alone.—All cases must have been treated by radical excision of the breast, and cases in which the operation was less extensive were excluded. To permit of fair comparison with the next group post-operative deaths were also excluded.

Operation and Post-operative Radiotherapy.—In this group cases having less extensive operations, such as simple mastectomy and even local removal of the tumour from the breast, were included provided that a full course of radiotherapy was given subsequently. Full treatment by radiotherapy was considered to be the delivery of a minimum dose of not less than 3500 r. in three weeks to the chest wall and to the whole length of the chain of glands from the axilla to the supraclavicular region on the affected side. In the majority of cases a minimum dose of 4500 r. was delivered to this area in a period of four weeks.

It was found that no useful purpose was served by making a comparison of the cases in Stage IV, for no matter what method of treatment was used, nearly all the cases died in the first few years. In any case, in a high proportion of cases the disease was so advanced that no treatment was given at all, or else the treatment was on a purely palliative basis and was designed to relieve pain and to diminish the extent of ulceration.

Basis of Comparison.—The commonly selected basis of comparison in carcinoma of any site is the five-year survival-rate. On such a basis progress must, however, be slow because of the delay which must occur before the results are available. Accordingly an attempt was made to obtain a more rapid means of evaluation, and it was found that if a patient remained free from recurrence for a period of three years that she was likely to be alive at the end of five years. The following figures show how remarkably the two sets of figures agree.

It must be emphasised that the symptom-free rate is used in a special sense and is taken to indicate that the patient was symptom free for three years, and not merely symptom-free at the end of this period. The three-year symptom-free rate has certain advantages over the five-year survival-rate, as is shown

Paget's Disease of the nipple is accepted as a primary duct carcinoma and regarded as Stage I unless palpable glands are present.

Total Cases.—For the period 1930 to 1942 there are available in the Radiotherapy Department the records of 1879 cases of carcinoma of the breast. When these cases are arranged according to the above method of staging the findings are as follows :—

TABLE I

Carcinoma Breast—1930 to 1942

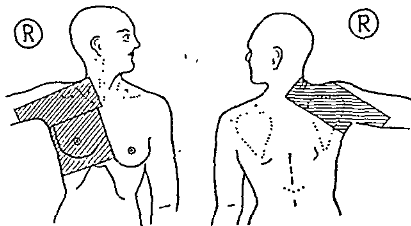
Year	Stage I	Stage II	Stage III.	Stage IV.	Recurrent Carcinomata	Unstaged.	Total.
1930	33	18	17	1	3	0	72
1931	21	22	21	6	2	0	72
1932	31	12	28	1	6	0	78
1933	19	20	37	8	5	3	92
1934	34	14	30	19	14	1	112
1935	34	22	15	39	14	3	127
1936	39	16	23	28	20	1	127
1937	50	19	32	36	32	2	171
1938	48	17	29	38	27	1	160
1939	45	24	27	42	31	3	172
1940	50	39	31	40	13	2	175
1941	69	49	42	66	25	2	253
1942	83	53	42	76	14	0	268
Total .	556	325	374	400	206	18	. 1879
Per cent. of total .	30%	17%	20%	21%	11%	1%	100%

Up till 1935 untreated and incompletely treated cases were not fully recorded.

The group termed "recurrent carcinomata" indicates cases treated outside the centre and only referred to the centre after recurrence has taken place.

The "unstaged" group refers to cases treated outside the centre and still remaining free from recurrence, but referred to the centre for observation. This group also includes a few cases in which insufficient information was available to permit of staging.

be referred to subsequently as the "treatable area." It will be obvious immediately that radiotherapy can only influence



results in so far as it can destroy cells left behind in the "treatable area," and that it cannot influence results if the disease has spread beyond the "treatable area."

TABLE III

New Recurrences in the "Treatable Area" expressed as a Percentage of the Total Cases Treated One, Two and Three Years Ago

			Number of Cases.			Percentage		
			One Year	Two Years	Three Years.	One Year	Two Years.	Three Years.
						Per Cent.	Per Cent.	Per Cent.
Stage I	Radical Surgery	Recurrences / Total Cases	22 / 165	9 / 163	7 / 153	13·3	5·5	4·6
	Surgery plus Radiotherapy	Recurrences / Total Cases	4 / 202	3 / 132	1 / 93	2·0	2·3	1·1
Stage II	Radical Surgery	Recurrences / Total Cases	18 / 84	5 / 83	6 / 80	21·4	6·0	7·5
	Surgery plus Radiotherapy	Recurrences / Total Cases	6 / 139	7 / 87	2 / 52	4·3	8·0	3·8
Stage III	Radical Surgery	Recurrences / Total Cases	30 / 107	5 / 107	2 / 101	28·0	4·7	2·0
	Surgery plus Radiotherapy	Recurrences / Total Cases	4 / 110	6 / 68	1 / 48	3·6	8·8	2·1

by the following example. Case 1794 had a radical excision of the breast on 30.5.36. In 1937 the patient developed several recurrences on the chest wall. On 3.8 37 these recurrences were

TABLE II

Comparison of Three-Year Symptom-Free Rate and Five-Year Survival-Rate (1930 to 1937 Cases)

	No. of Cases	Three-Year Symptom-Free Rate	Five-Year Survival-Rate
		Per Cent.	Per Cent.
Stage I .	247	54	52
Stage II .	136	34	34
Stage III .	183	20	20
Total .	566	38	37

treated by means of X-rays and the patient is still alive and free from disease. The patient was thus alive at the end of five years, but could scarcely be considered to be alive as the result of operation alone. By means of the three-year symptom-free rate this case would be recorded as a surgical failure, while the five-year survival-rate actually indicates the case as a surgical success. The example also demonstrates that only the first-planned treatment can be usefully analysed. The five-year symptom-free rate would be a still more valuable means of assessment, but as the number of patients treated by post-operative radiotherapy five years ago is small, the three-year symptom-free rate, as defined, has been selected as the basis of comparison.

Recurrence - Rate in the "Treatable Area." — Before passing to the consideration of the three-year symptom-free rates, it is of interest to try to visualise the possible affects produced by post-operative radiotherapy.

Successful treatment of a patient by radical surgery alone implies complete removal of all disease locally from the chest wall and from the axilla, and also implies that malignant cells have not been disseminated beyond this area. Failure to cure the patient may be due to malignant cells having been left behind locally or to distant dissemination.

The area treated by radiotherapy, in this series of cases to be discussed, is more extensive than the area treated by radical surgery, and includes not only the chest wall and the axilla but also the supraclavicular region. This more extensive area will

included in the above clinical Stage I, and the number of recurrences would have been considerably less in this stage. (Of 215 cases in clinical Stage I, 49 per cent. were found to have involvement of the axillary glands on histological examination.)

The Symptom-Free Rates in Stages I, II and III. The reduction in the local recurrence-rate is considerable in all stages, and it is, therefore, to be expected that post-operative radiotherapy should result in an increase in the three-year symptom-free rate.

The results in Table IV at the three-year period are what might be expected from a study of the total recurrence-rates in Table III.

TABLE V

Recurrence-Rates in the "Treatable Area" and Symptom-Free Rates

		Total Recurrence-Rate at Three Years	Symptom Free Rate at Three Years
		Per Cent.	Per Cent
Stage I	Radical Surgery	23 4	54
	Surgery plus Radiotherapy	5 4	76
	Difference	18 0	22
Stage II	Radical Surgery	34 9	28
	Surgery plus Radiotherapy	16 1	60
	Difference	18 8	32
Stage III	Radical Surgery	34 7	21
	Surgery plus Radiotherapy	14 5	44
	Difference	20 2	23

In the above table the difference in the total recurrence-rates in three years bears some relationship to the difference in the symptom-free rates obtained by the two methods of treatment.

The Symptom-Free Rates with and without Involvement of the Axillary Glands.—The Steinthal method of staging has already been mentioned, and it was noted that this method of staging was dependent on the histological examination of the axillary glands. The effect of secondary involvement of the axillary glands is considerable, and it was thought advisable to re-group the cases in the above three clinical stages into two groups—those without histological involvement of the axillary glands and those with involvement—and to compare again the results from radical surgery alone and from surgery combined with post-operative radiotherapy. Unfortunately histological examination of the axillary glands was not always carried out, and the number of cases available for comparison is smaller.

The first point to be determined, therefore, is how often are malignant cells left behind in the "treatable area" after the radical operation. It is, of course, quite impossible to determine this point directly, but some indication of its frequency may be deduced by noting how often recurrences become manifest at a later date in this area. By the same means the effectiveness of post-operative radiotherapy may be determined.

The recurrence-rates in the "treatable area" after radical surgery alone are high in all three stages. It is important to bear in mind that the method of staging is not that usually employed—namely the Steinthal method. In the Steinthal method cases are only placed in Stage I provided that there is no involvement of the skin and provided that the axillary glands on histological examination were free from secondary deposits.

TABLE IV

Comparison of Results between Radical Surgery and Surgery plus Post-Operative Radiotherapy

			Number of Cases			Percentage Symptom-Free		
			One Year	Two Years	Three Years	One Year	Two Years	Three Years
						Per Cent	Per Cent	Per Cent
Stage I	Radical Surgery	Symptom-Free Total Cases	124 165	107 163	83 153	75	66	54
	Surgery plus Radio-therapy	Symptom-Free Total cases	180 202	103 132	71 93	89	78	76
Stage II	Radical Surgery	Symptom-Free Total Cases .	52 84	35 83	22 80	62	42	28
	Surgery plus Radio-therapy	Symptom-Free Total Cases	116 139	57 87	31 52	83	66	60
Stage III	Radical Surgery	Symptom-Free Total Cases	50 107	31 107	21 101	47	29	21
	Surgery plus Radio-therapy	Symptom-Free Total cases	93 110	37 68	21 48	85	54	44

Dr A C Aitken has kindly examined the figures in this table and is satisfied that the difference in the results is statistically significant.

If the cases had been staged by the Steinthal method the number of cases in Stage I would have been approximately half that

radiotherapy. Since 1939 (*i.e.* the period 1940 to 1942), 95 per cent. of all cases in Stages I, II and III have received

TABLE VII

Comparison of Results between the periods 1930 to 1934 and 1935 to 1939. All Cases in Stages I, II and III (Post-Operative Deaths excluded)

		Three-Year Symptom Free Rates.		Percentage of Cases receiving Full Post-Operative Radiotherapy, 1935 to 1939.
		1930 to 1934	*1935 to 1939*	Per Cent.
Stage I	Total Cases Symptom-Free	131 53 per cent.	201 62 per cent.	45
Stage II	Total Cases Symptom-Free	80 26 per cent.	94 40 per cent	52
Stage III	Total Cases Symptom-Free	120 19 per cent.	114 32 per cent.	41
Stages I, II and III	Total Cases Symptom-Free	331 34 per cent	409 49 per cent.	45

full post-operative radiotherapy, so that in the future still greater improvement may be expected.

Present Methods.—The difference in the symptom-free rates when the glands are histologically involved suggests that, as shown in Table VI, post-operative radiotherapy may be relied upon to destroy the malignant cells left behind in the axilla, for the results are almost twice as high when post-operative radiotherapy was given.

Complete removal of secondarily involved axillary glands by surgery is never an easy matter, and even with the greatest care malignant cells may be left behind in the wound. Following the operation considerable serous exudate pours into the area, and as this exudate is absorbed malignant cells may escape to distant sites and may, therefore, spread beyond the "treatable area." When distant dissemination has thus occurred post-operative radiotherapy is rendered ineffective.

Consequent upon these observations it was agreed that, for a time at least, the breast alone should be removed by surgery and that the axilla should not be dissected, and that all cases so treated surgically should have a full course of radiotherapy. It is still much too early to evaluate the results, and the following one-year symptom-free rates are put forward with some hesitation

The recurrence-rates in the "treatable area," the symptom-free rates in each stage and the symptom-free rates according to

TABLE VI

Comparison of Results between Radical Surgery and Surgery plus Post-Operative Radiotherapy

Stages I, II and III. Axillary Glands Histologically Examined

			Number of Cases.			Percentage Symptom-Free.		
			One Year	Two Years	Three Years	One Year.	Two Years.	Three Years.
						Per Cent.	Per Cent	Per Cent
Glands Histo-logically Negative	Radical Surgery	Symptom-Free Total Cases	65 79	53 78	42 74	82	68	57
	Surgery plus Radio-therapy	Symptom-Free Total Cases	85 87	58 64	39 43	98	91	91
Glands Histo-logically Involved	Radical Surgery	Symptom-Free Total Cases	77 143	52 141	33 135	54	37	24
	Surgery plus Radio-therapy	Symptom-Free Total Cases	160 197	85 151	50 100	81	56	50

whether the axillary glands were involved or not, all show that effective post-operative radiotherapy results in considerably improved symptom-free rates and, therefore, in higher five-year survival-rates. Up until 1941 the decision to treat or not to treat cases by post-operative radiotherapy, rested with the surgeon in charge of the case, and it may be assumed that there was no selection of early cases for radiotherapy. If anything, the reverse was the case. A further point in demonstrating that the better results in the surgery plus radiotherapy group were not obtained by selection is the fact that the results obtained in all cases in Stage I, II and III have improved since the present method of radiotherapy was introduced in 1935

The improvement in the three-year symptom-free rates is sufficiently great to show that the use of post-operative radiotherapy has, in fact, led to better results and proves, too, that the improvement shown in Tables IV and VI was not obtained by selection.

It should be noted, too, that only 45 per cent. of the total cases in the period 1935 to 1939 received full post-operative

afraid of the outcome when a diagnosis of cancer is made, for of the 2000 cases of cancer in all sites occurring per 1,000,000 of the population, 1700 die of cancer. The medical outlook must first change before propaganda to the public is introduced, because if patients did seek advice at an earlier stage, in many cases they would be assured that the condition was not serious, and because they naturally wish to believe this, they might not seek advice again till an even later stage than at present. As in cancer so in other diseases, early diagnosis and treatment are of paramount importance, and every effort must be made to bring this about in the near future. It cannot be too strongly emphasised that there is no credit attached to the making of a diagnosis when all the classical signs and symptoms are present and that such a diagnosis is nearly always a "pre-death-certificate diagnosis."

Provided that patients do come to be treated earlier, I see no reason why, at the very least, one out of every two of all cases of cancer of the breast (all four stages) should not be permanently cured. It is important to realise that this high figure is easily obtainable with the methods of treatment at present available (surgery and radiotherapy).

Summary

1. Of the women who develop cancer, one in four develops the disease in the breast.

2. In this series the average age of the patient when treated was 55·5 years.

3. Under existing conditions, and when surgery is the only method of treatment available, probably not more than one in five of *all cases* of cancer of the breast survive five years.

4. The three-year symptom-free rate (as defined) is not only a reliable guide to the five-year survival-rate, but its adoption permits of progress being made more rapidly.

5. A total of 1879 cases has been analysed, and in the operable group (stages I, II and III) effective post-operative radiotherapy, by destroying cells left behind in the "treatable area," results in much higher three-year symptom-free rates in all three stages.

6. Post-operative radiotherapy is still effective when the disease has spread to the axillary glands, but is of no value so far as survival-rate is concerned if the disease has spread to distant sites.

Owing to the teaching of the past and to the fact that it is impossible for the average general practitioner to gain adequate experience in the diagnosis of cancer of the breast, it far too often happens that *the early case is wrongly diagnosed* as a cyst, a simple tumour, or an area of chronic mastitis. Textbooks all too often describe only the advanced stages of the disease, and it is common to find, prominently displayed, a long list of differential diagnoses so set out as to indicate that a differential diagnosis is possible in all cases. It cannot be too strongly emphasised that, in many cases, the features of an early cancer of the breast are identical with those of a cyst or simple tumour. In the early stages a carcinoma is a mobile tumour within the breast and there is no enlargement of the axillary lymph nodes. Differential diagnosis with any degree of certainty is only possible when the cancer has reached an advanced stage. The diagnosis of cancer of the breast is, therefore, histological in the early stage of the disease—the stage at which treatment gives highly successful results.

Any tumour of the breast must be regarded as carcinoma until it is removed and histologically proven otherwise. The age of the patient is not always a reliable guide, for in this series one in every twelve patients were found to be under forty years of age. To wait till the period of clinical certainty is reached, when the disease shows all the so-called classical signs of its presence, is perhaps of value so far as the signing of the death certificate is concerned, but it is of little value to the patient. A diagnosis must be made at the curative stage and not at the pre-death-certificate stage if better results are to be obtained in cancer of the breast as a whole. It follows, too, that the existing organisation for treatment must be altered so that hospital waiting-lists for malignant disease are abolished. Until this is possible it is important that early cases should be given preference in admission, and that preference should not be given to the late cases as so often happens at present.

So far as the patient's delay is concerned, I feel sure that this will become less as soon as the public come to realise that cancer of the breast can be cured in a high proportion of cases. Reorientation of the medical outlook in the direction indicated above, and the better results consequent upon this, will do much to diminish the patient's delay, because the fear which exists at present as to the ultimate outcome will no longer be justified.

Under present conditions the public is justified in being

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